The Role of Aβ in the Development of Alzheimer's Disease and its Mechanisms

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Abstract. Alzheimer's disease (AD) is chronic neurodegenerative dementia representing the most common cause of dementia in the elderly population. It is a major source of morbidity, mortality, and healthcare expenditure worldwide. Although the molecular and cellular properties related to AD have been demonstrated decades before the onset of clinical symptoms, AD's pathogenesis is still unknown as a combination of risk factors causes it. Today, pathogenesis theories focused on senile plaques (SP) formed by the extracellular accumulation and deposition of Aβ peptides and neurofibrillary tangles (NFTs), which are composed of the hyperphosphorylated tau protein. Furthermore, growing evidence points out that toxic Aβ plays a primary causal role in the induction and transmission of pathology and neuronal dysfunction and loss. Therefore, Aβ is crucial to the development of AD and is a noteworthy issue in AD research. This review shows the formation of Aβ and the differences of cytotoxicity of its various isoforms and aggregation states. It also summarizes the mechanisms by which Aβ induce AD through its neurotoxicity and state how these mechanisms interact and reinforce each other.

1 Introduction

Alzheimer's Disease(AD) is one of the most well-known neurodegenerative diseases, and it is currently the fourth most common cause of death in the United State [1]. It is estimated that AD affects over 12 million individuals worldwide and is the leading cause of dementia in people over 60 [2]. As the global population ages, AD is placing an increasing burden on society. Although it is possible to slow the disease's progression, there are presently no cures for AD because the mystery behind the understanding of its cellular, molecular, and pathological initiation and development is not clear [3]. It is now generally accepted in the scientific community that AD has three characteristic pathological changes: senile plaques(SP), neurofibrillary tangles (NFTs), and the loss of neurons. Aβ is directly involved in causing one of the key pathological features of AD, SP [4]. Massive evidence has manifested that the overrun of formation and deposition of Aβ causes neurodegenerative cascade resulting in synaptic dysfunction, neuronal loss [5]. Besides, substantial data indicate that the solubility of Aβ, and the quantity of Aβ in different pools, maybe more closely related to the disease state. The composition of these pools of Aβ reflects different amyloid deposits and has definite correlates with the patient's clinical status. These facts proved that Aβ is recognized as a primary initiating factor in the pathogenesis of AD. This review suggests how abnormalities in the AD brain form Aβ, highlight the importance of differentiating between various species of Aβ, and summarize the many mechanisms by which Aβ triggers AD in cellular and molecular levels.

2 Overview of Alzheimer's Disease

2.1 Introduction of AD

Alzheimer's Disease(AD), as one of the most prevailing neurodegenerative disorders, has a devastating effect on elderly people. It brings about multifactorial pathological changes in the brain. AD is first described in 1907 by Dr.Alois Azheimer. There are two forms of Alzheimer's disease: an early-onset version caused by an autosomal dominant mutation, and a sporadic form of the disease. AD's clinical manifestation is a gradual loss of memory and cognitive functions where episodic memory is affected first, followed by executive functions, semantic memory, language, and spatial orientation skill deterioration [6]. Statistically, about 44.4 million people over 65 worldwide are suffering from dementia, and 70 percent of them are Alzheimer patients. Research predicts that that number will probably cross 135 million by 2050 [7]. In addition, AD affect approximately 5.2 million elderly peoples in America and 10 million people in China aged over 65.

2.2 Risks factors and pathological hallmarks

The major risks factors now identified for AD include advance ages, low educational level, genetic factors, chronic infection, immunodeficiency, impaired

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metabolism and reduced endocrine secretion [8]. AD's pathological hallmarks include SP (senile plaques), neurofibrillary tangles (NFTs), synaptic failure, and neuronal loss in AD sensitive brain regions such as the hippocampus, neocortex, and nucleus basalis of Meynert. Further researches have shown that SP (senile plaques) formed by extracellular and intracellular deposition of amyloid-beta (Aβ) and into-neuronal NFT consisting of aggregates of hyperphosphorylated tau protein. Thus, the etiology of AD has formed there major research areas: deposition of Aβ, tau protein, and the mechanism of neuronal loss. Moreover, the three primary hypotheses derived are the amyloid cascade hypothesis, tau hyperphosphatation, and cholinergic injury hypothesis.

3 Styling Amyloid precursor protein

Amyloid Precursor Protein (APP) is the precursor of Aβ peptide, encoded by a gene in chromosome 21 [9]. It is a type I transmembrane glycoprotein, with a long N-terminal domain and a cytoplasmic C-terminal domain. APP can be found in different types of cells, including neurons and astrocytes [10]. It plays an essential role in many important activities such as brain development, memory and synaptic plasticity.

After post-translational modification, APP is processed in one of the two main processing pathways - the non-amyloidogenic or the amyloidogenic [11]. In normal cells, APP is hydrolyzed via the non-amyloidogenic pathway, which is the predominant way. Non-amyloidogenic processing is characterized by the non-production of Aβ peptide [12]. APP is first sectioned by α-secretase and then by γ-secretase to produce APPα and the 83 amino acid CTFα, which is then rapidly cleaved to generate the p3 fragment that is non-toxic [13]. In the abnormal cells of patients with AD, APP is hydrolyzed by the amyloidogenic pathway, which occurs to a minor extent [14]. The production of Aβ peptide characterizes amyloidogenic processing. APP is sequentially cleaved by β-secretase and γ-secretase. β-secretase first cleaved the peptide bond between Met671 and Asp672 to release a large secreted derivative, sAPPβ, and a fragment of 99 amino acids, CTFβ [15]. Subsequent γ-secretase cleavage of this remaining APP membrane-bounded carboxyl-terminal fragment, releasing the Aβ peptide and the AICD fragment. The third way of APP cleavage has been recently discovered as well. The physiological functions of this processing pathway still need to be evaluated. Still, the speculation that it may be involved in modulation of neuronal activity and synaptic plasticity is an intriguing direction for AD study [16]. It involves η-secretase that cleaves APP at amino acids 504–505 and leads to the generation of the higher molecular mass carboxy-terminal fragments Aη-α and Aη-β, after second cleavage by α- and β-secretase, respectively. The first one, Aη-α with the Aβ1–16 peptide included in its sequence was reported to be neurotoxic.

4 Amyloid beta peptide

Amyloid beta (Aβ) is a 38 to 43 amino acid peptide with about 4.0-4.2 kDa molecular weight. The native conformation of Aβ has almost no secondary structure, so it is considered a natural unfolded protein [17]. It exhibits a high propensity to be misfolded and chemically sticky [18]. Hence, Aβ forms soluble oligomers and fibrils by folding from the original random-coil rich state to an α-helical rich intermediate, and finally to a β-sheet monomer that self-assembles into soluble Aβ oligomers, which further aggregate to form insoluble Aβ fibrils [19].

From Aβ1–38 to Aβ1–43, several lengths of the peptide can be released based on the exact location of the cleavage by γ-secretase in humans. The different molecular lengths of various isoforms of Aβ peptides are due to their C-terminal [20]. Furthermore, monomeric Aβ peptides encompass full-length, and numerous N-terminal truncated isoforms as well [21]. The most abundant species generated in the AD brains is Aβ40 at about 80-90%, followed by Aβ42 that accounts for 5-10%. As the last few amino acid, residues at the C-terminal of Aβ are highly hydrophobic, the longer the C-terminal, the easier peptides to deposit. This shows the slightly longer forms of Aβ, particularly Aβ42, are more likely to make fibrillar structures from proteins that fold into an alternative, β-rich form, therefore Aβ42 is the principal species deposited in the brain [22]. Other studies have suggested that other Aβ isoforms, including Aβ8, Aβ16, Aβ37, Aβ38, Aβ43, and Aβ56 produced by APP degradation may also be related to AD [23].

5 The amyloid cascade hypothesis

Initially suggested in 1992, the Amyloid Cascade hypothesis is an effective way to link Aβ to AD, and has catalyzed much research in this area [24]. This theory suggests that what triggers neuronal degradation initially in Alzheimer's disease is enhanced amyloid-β generation and aggregation (see Fig 1) [25]. It suggested that if the amount of Aβ generated is greater than the amount that is degraded, accumulation occurs, resulting in the generation of neuroinflammatory plaques, which enables to induce NFT formation, neuron loss, vascular damage, and the associated symptoms of AD through the cytotoxicity of Aβ [26]. Currently, the most widely accepted hypothesis after modifying including the following five cascade reaction processes: the deposition of Aβ generates abnormal increase of Aβ, insoluble plaque SP, then the immune reactions and oxidative stress are triggered because SP activates microglia and astrocytes, next the series of reactions lead to incorrect phosphorylation of Tau protein and formation of NFT, eventually causing AD [27].

What's more, recent key researches have made a critical modification of the hypothesis. It emphasized soluble Aβ oligomers are the most cytotoxic one of three distinct pools of Aβ species, Aβ monomers, soluble Aβ oligomers, and insoluble fibrillar Aβ [28]. The close linkage between Aβ oligomers and neurodegenerative

processes of AD has also been discovered [29]. This will be described in more detail later.

In addition, it's worth noticing that the current conception of the amyloid cascade hypothesis is based on in vitro studies, which are generally carried out at higher concentrations than found in vivo [30]. Due to the formation of various Aβ species is influenced by unpredictable variables on account of existing techniques don't have enough ability to fully simulate the stable environment in vivo [31]. Therefore, careful consideration should be given to inferring the actual situation in vivo from the conclusions of in vitro studies.

Furthermore, there have been challenges in the nearly 30 years since this hypothesis was proposed, as the exact link between the number of amyloid plaques comprising primarily Aβ peptides and dementia is still unclear. The finding that Aβ also appears in people's brains without symptoms of cognitive impairment is the basis for the argument [32].

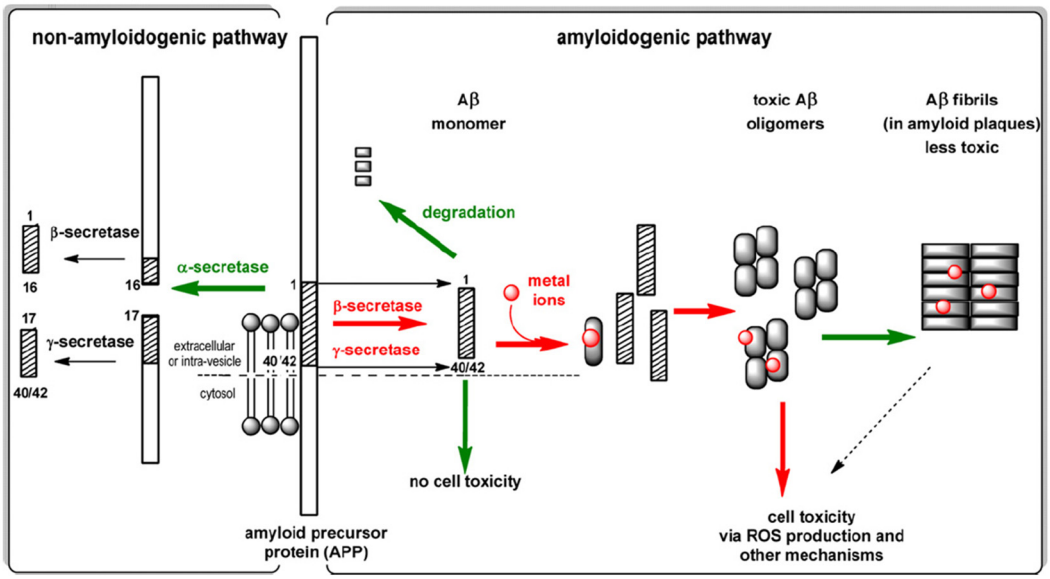

Fig1. A schematic view of the amyloid cascade [25].

6 The degree of cytotoxicity of three main states of Aβ

6.1 Monomers

As mentioned above, Aβ40 and Aβ42 are considered as the main disease-causing species among the Aβ species present in AD. Moreover, there is growing evidence that the formation and reproduction of misfolded assemble of Aβ42 rather than the more abundant Aβ40, triggers the Alzheimer's cascade. The close correlation between the ratio of Aβ42/40 and the age of disease onset in familial AD is a good illustration of this. Aβ42 is commonly considered to be the most pathogenic isoforms which exhibit higher toxicity and aggregation propensity. The reason for Aβ42 is more cytotoxic than Aβ 40 is currently believed that two isoforms have varying three-dimensional structures even though only subtle differences in sequences [33].

During the formation of Aβ monomers, if the sites between Val711 and Ile712 are sliced, they will form Aβ40. If γ-secretase is used to slice the sites between Ala713 and Thr714, Aβ42 will be generated.

An experiment about the initial efforts of MD-optimized modeling suggested that with the SSNMR distance constraints, Lys28 could not maintain a salt bridge with Asp23, which was observed for many models of Aβ40.[41] At the same time, the experiment that measured intra-molecular 13C–15N distance was 4.0 Å ± 0.1 Å suggested the formation of a unique salt bridge between Lys28 and Ala42 [34]. This salt bridge's stabilization explained why the unique S-shaped triple-β sheet motif is only observed for Aβ42 fibrils. On the contrary, Aβ40 lacks Ala42 to form these salt bridges. Due to salt bridges between Lys28 and Ala42 are much more stable than those between Lys28 and Asp23, thus, Aβ42 has relatively higher conformational stability, exposing more hydrophobic C-terminal that contributes to the change in hydrophobic interaction patterns, which promotes Aβ42 has a much stronger aggregation propensity that is more likely to assemble into oligomer and fibrils [35].

Additionally, recent research also found that the interaction with the membrane dramatically changes the conformation of Aβ42 monomers,characterized the aggregation of Aβ42 at its physiologically relevant low concentration (10 nM), which causes the transition of Aβ42 into the aggregation-prone, misfolded conformations. And such transition triggers the self-assembly into soluble oligomers, which exhibits the highest cytotoxicity. This offered a new approach that slows Alzheimer's cascade by turning Aβ42 into Aβ40.

Studies have also found that Aβ40 and Aβ42 can form oligomers with different molecular masses. Findings show that Aβ40 oligomers reached maximum size at the tetramer level and Aβ42 was capable of producing much larger oligomers because of the hydrophobic GxxxG motif existed in the amino acid sequence of Aβ42 that is vital for dimerization [36].The substitution of Gly33 for

the more hydrophobic residues of either alanine or isoleucine within the dimerization motif resulted in the ability to form high MW oligomers.

Another study used single touch atomic force microscopy (AFM) has established that monomeric Aβ42 forms two different types of oligomers -low molecular weight (MW) oligomers with heights of 1–2 nm and high MW oligomers with heights of 3–5 nm. Also, it has suggested that the low MW oligomers composed of Aβ42 are able to stack to form the high MW oligomers due to the similar diameters they showed. The different degrees of harm of influence of high MW oligomers and low MW oligomers will be talked later.

Furthermore, an experiment that studied three solutions: (1) Aβ40, (2) Aβ42, and (3) a mixture of Aβ40 and Aβ42 has found that Aβ40 has a capability of suppressing the formation of the high MW oligomers formed by Aβ42. This finding can serve as an evidence supporting the theory that the ratio of Aβ40 to Aβ42 is an important factor of risk for AD.

Aβ40 and Aβ42 make up two different forms of fibrillar Aβ present in AD brain separately: cerebral vascular amyloid plaques that are primarily composed of Aβ40 and parenchymal amyloid plaques that are primarily composed of Aβ42 [37]. Despite the higher plasma Aβ40 level, the Aβ42 fibril is the initial and predominant constituent of amyloid plaques. For example, antibodies were identified that appear to selectively recognize vascular amyloid and not parenchymal amyloid. On the other hand, a recent study on transgenic mice established that early-onset parenchymal amyloid plaques impact the development of vascular amyloid by serving as a scaffold. The reason for the phenomenon is believed to be that there are significant structural differences involving in misfolded Aβ42 and Aβ40 in AD.

Researches have established atomic structural models for structurally homogeneous Aβ42 fibril samples and found that structural features of it differ from Aβ40 fibril shown in previous work [38]. The data based on SSNMR (solid-state NMR) displays a unique S-shaped triple-β motif, which is made of three β-sheets encompassing residues 12–18 (β1), 24–33 (β2), and 36–40 (β3). And for Aβ40 fibril, most of these structures are characterized by a U-shaped β–loop–β motif, where a single curved loop region connects two stretches of parallel β-sheets (between residues Asp23 and Gly29), with many stabilized by a salt-bridge between Asp23 and Lys28 side-chains [39].

These investigations provided an innovation view in the past view that considered fibrils of Aβ40 and Aβ42 to be similar. Overall, the reason why Aβ42 and Aβ40 oligomerize through distinct pathways was explained by major differences in the stabilizing interactions between Aβ42 and Aβ40 fibrils, while offering a mechanistic clue to early-stage misfolding of Aβ [40].

6.2 Oligomers

The cytotoxicity of soluble Aβ oligomers was first highlighted in 1995 [41]. In subsequent decades, many studies have shown soluble Aβ oligomers to be the most toxic Aβ form. A study about the correlation between CSF(cerebrospinal fluid) levels of soluble Aβ oligomers and cognitive dysfunction characteristic of AD provided evidence proving Aβ oligomers are primarily associated with both synaptic dysfunction and causing neurodegenerative processes. Furthermore, the conclusion that Aβ oligomers preferentially interact with membranes compared with Aβ monomer has been proved by recent research about the investigation of interactions between Aβ peptides and hippocampal cell membranes [42].

Soluble Aβ oligomers are generally considered to have two size classifications, high-molecular-weight oligomers (high MW oligomers) and low-molecular-weight (low MW oligomers) oligomers. Low MW oligomers have been observed at ∼20 kDa, including dimers, trimers, and tetramers. High MW oligomers have been observed ranging from 90 to 650 kDa (20 to 150 mers). For instance, the most commonly observed high MW oligomer has a molecular mass of ∼56 kDa, corresponding to a dodecamer. All of soluble Aβ oligomer species have been reported to display synaptic toxicity. An opinion is that the high MW oligomers appear to be more toxic in vitro and in vivo compared to low MW oligomers. Research showed that the clearance of high MW Aβ oligomers is much slower compared with low MW Aβ species has supported the opinion [43]. This research also indicates that Aβ oligomers are more likely to accumulate in large quantities, resulting in damage in the brain.

6.3 Fibrils

Insoluble fibrillar Aβ, including parenchymal amyloid plaques and cerebral vascular amyloid is suggested as benign species that reveal relatively low toxicity [44]. The formation of Aβ fibril has been thought to be a mechanism for removing oligomers [45]. Another minority view believed that deposition of fibrillar Aβ themselves could physically disrupt cell membranes and further causing damage of cells and tissue architecture or have cytotoxic properties as well [46]. Moreover, studies have also supported that polymorphism, which exists in Aβ plaques due to exposure to different environmental conditions during growth, results in differing cytotoxic pathways and cytotoxicity levels. The polymorphic structure of AD brain Aβ can be indicated since it is much more efficient at seeding Aβ fibril formation when injected into the brains of transgenic mice producing Aβ peptide than are equivalent amounts of synthetic Aβ fibrils or Aβ extracts from plaque-containing transgenic mouse brains. The changes in cytotoxicity are thought to be affected by variations in molecular structures of the fibrils formed, hence different amino acid residues would be exposed, leading to different cytotoxicity levels. A well example is that fibrillar Aβ, but not soluble Aβ, is specifically toxic to cultured neurons in vitro [47]. Hence, whether the low level of toxicity of fibrillar Aβ have effects on the development of early AD or not remains to be proven.

6.4 Mechanism Linkage among oligomers and fibrils

As the preceding part of the text that the amyloid fibrils themselves are relatively inert and may comparatively exhibit low cytotoxicity [48]. Nevertheless, Aβ fibrils can still be harmful considered from another aspect. Several studies have indicated the mechanism linkage among Aβ fibrils and Aβ oligomers and suggested Aβ plaques are a source/sink for the most cytotoxic Aβ oligomers [49].

It has been established that the level of Aβ monomer and deposited plaques in the patients' brain is several orders of magnitude higher than the level of soluble Aβ oligomers, but the degree to which oligomers, as intermediate forms from monomers to fibers, convert to each other remains unclear. There is already evidence that though both soluble oligomer formation and fibril formation have to pass through multimeric stages they may not be taking the same pathways [50]. Some breakthrough reports established that fibrillar Aβ may catalyze oligomerization of Aβ monomers leads to the rise of oligomers, causing growth of Aβ plaques. The disaggregation may not be a route for fibrillar Aβ converting in oligomers [51]. Besides, other studies about transgenic mouse models of AD supported that the symptoms of neurodegeneration lighted with the decrease of Aβ oligomers content and the increase of Aβ plaques content [52]. This provided evidence showing that Aβ plaques may be a sink of oligomers [53]. Hence, the debating relationship between Aβ plaque and Aβ oligomers is still a valuable research direction of AD.

7 Cytotoxic effects of Aβ

The review that mentioned the amyloid Aβ cascade hypothesis holds that Aβ is deposited in the brain under pathological condition, triggering AD by damaging neurons via the cytotoxicity effects of Aβ. The cytotoxic effects of Aβ species mainly include the following five aspects.

7.1 Oxidative stress

Oxidative stress refers to the effect of the oxidation system beyond the restriction of the anti-oxidant defense mechanism, which is driven by both amyloid-dependent and amyloid-independent mechanisms [54]. It is one of the primary ways to induce neuronal damage.

The key steps of oxidative stress is the generation of reactive oxygen species (ROS). ROS are widely defined as oxygen-containing chemicals with reactive properties. Under normal circumstances, they are kept at a low level and are necessary to maintain the homeostasis in cells and play an important role in signaling [55].Therefore, they are not fully eliminated and their total suppression is detrimental. Under pathological condition, excess ROS are produced in the body and accumulated at a too high level. This phenomenon is dangerous because it is accompanied by high cytotoxicity, and it can occur either by an overproduction or an insufficient elimination of ROS. ROS are generated continuously in cells because of oxidative biochemical reactions, which produce unstable cytotoxic molecules known as free radicals under physiological conditions. Several types of ROS with different structures involve in the AD like superoxide anion (O2-), hydroxyl radical (HO-) and hydrogen peroxide (H2O2) [56]. Normally, complex properties of oxidative stress are presented in Alzheimer's brains: lipid peroxidation, increasing protein, DNA and RNA oxidation and impaired mitochondrial function, since these ROS have incomplete electron orbitals [57].

Several pieces of evidence suggest that oxidative stress occurs early in the course of AD, which would support its role in AD pathogenesis, in relation with the presence of Aβ [58]. For example, elevated levels of Aβ40 and Aβ42 have been reported to be associated with increased levels of oxidation products from proteins, lipids and nucleic acids in AD hippocampus and cortex [59]. By contrast, brain regions with low Aβ levels did not present high concentrations of oxidative stress markers.

The relationship between enhancive ROS production and Aβ has been established. Reviews summarized that Aβ can bound to redox active metal ions, including Zn(II), Cu(II), Cu(I) and Fe(II) ,to catalyze the production of ROS [60]. A research has found Fe(III) does not form a stable complex with Aβ because it finally converts into Fe(III)(HO)3 and precipitates, which has shown ROS production by Fe(III) and Aβ is unlikely [61]. However, an experiment about iron toxicity also suggested that Aβ binds with Fe(III) to reduce it into Fe(II) and H2O2. And this is thought to be a way for Aβ to induce ROS production [62]. In addition, Aβ activate microglia and astrocytes to boost the release of ROS by both [63]. Furthermore, Aβ activates cdk5, which may induce oxidative stress by generation of ROS. This is related to Cdk5 phosphorylates [64]. An alternative way for Aβ to trigger generation of ROS is by shaking up the electron transport chain. This results in shrinking the activities of cytochrome oxidase which is the key enzymes for electron transport and the deficiency of it generate ROS. Some works has also demonstrated that Aβ accumulation within the mitochondria directly interacts with ABAD and cyclophilin D, promoting ROS leakage as well membrane potential change, and Ca2+ dysregulation [65]. Last, changes in Ca2+ homeostasis mediated by mitochondria and endoplasmic reticulum may be the basis for inducing Aβ cytotoxicity [66]. As a result, intracellular Aβ oligomers modulates resting cytosolic free Ca2+ levels, remodels intra-organellar Ca2+ by disruption of mitochondria-associated ER membranes, alters Ca2+ release from internal stores, which can lead to ROS formation. Likewise, it has been reported extracellular actions of Aβ oligomers effects ROS production by binding to N-Methyl D-Aspartate receptor (NMDAr) on excitatory synapses.

In general, Aβ promotes ROS production and are further responsible for oxidative stress via trace element interactions, mitochondrial dysfunction as wll Ca2+ perturbation. Thus, affecting the progression and severity.

The relationship between Aβ and oxidative stress is not unipolar. Oxidative stress can enter into a vicious cycle, as Aβ-mediated production of ROS can destroy

biomolecules, which may lead to higher ROS accumulation.

Aβ can activate GK3β (glycogen synthase kinase-3beta) through want signaling pathway and Cdk5 (cyclin dependent kinase 5) by increasing the intracellular Ca2+ [67]. Previous studies have shown Cdk5 activates β-secretase and GSK3β activate both β-secretase and γ-secretase, hence they stimulate the increase of Aβ production, influencing its accumulation and formation of ROS in the AD brain. Oxidative stress induces RCAN1 (a regulator of Calcineurin1 gene) that can activate GSK3β [68]. Additionally, oxidative stress decreases the activity of α-secretase and increase the expression and activation of β-secretase and γ-secretase which are critical for the generation of Aβ from. The data about transgenic Tg2576 mice provided evidence for oxidative stress representing a major risk factor in causing Aß deposition [69]. These mechanisms are also related to hyperphosphorylation of tau. Furthermore, when ROS attacks metalloproteins, it can lead to the release of redox-competent metal ions with a subsequent increase of ROS production. When calcium homeostasis is disrupted, Aβ oligomerization is further promoted as well [69]. In other words, mitochondria are much more sensitive to oxidative stress. In addition to support synaptic transmission, mitochondria also has multiple pathways including maintaining appropriate regulating intracellular calcium homeostasis, regulating the production of reactive oxygen species (ROS), as well as synthesizing essential intermediates or final products of several neurotransmitters [69]. Thus, while the oxidative stress causing mitochondria dysfunction leads to further pathological oligomerization of Aβ and excess ROS production, it will continuously induce serious oxidative stress.

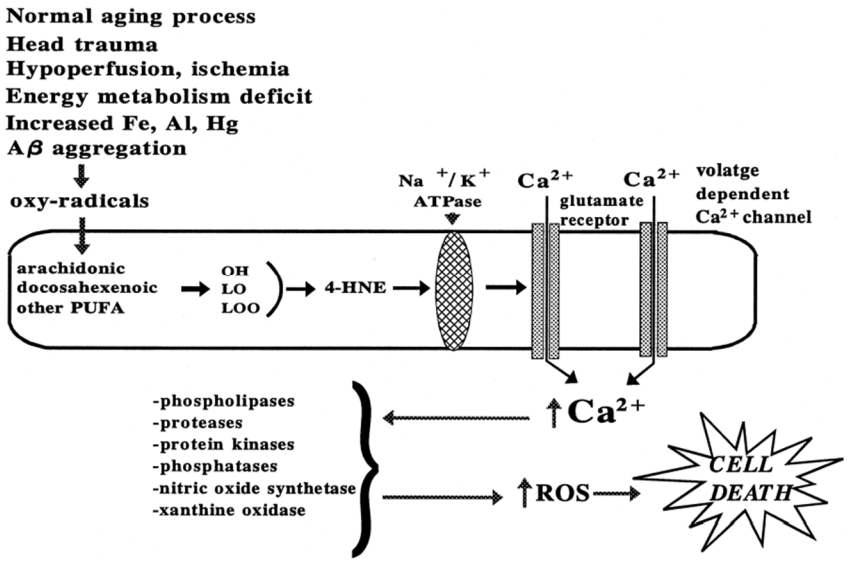

Fig2. A hypothetical mechanism of potential neuron death in AD [75].

7.2 Inflammation

There is accumulation of experimental evidence that AD has significant signs of inflammatory activity present in the brain [62]. Inflammation within the brain is a typical double-edged sword: it monitors both microglia and astrocytes positively associated with the activation of phagocytic activity to eliminate the debris and the pathogenic elements like Aβ that may trigger AD, while on the other hand, the glial activation induces the production of factors with harmful consequences for the neuronal system. In specific, the inflammation in AD is a sort of chronic reaction of the innate immune system causing facilitating Aβ deposition, neuronal loss and cognitive deficits, and further lead to AD [63].

The inflammation is caused by continued presence of Aβ accumulates [64]. For example, studies suggested that NPs (neurotic plaques) that consist of Aβ, activate the inflammatory response mediated by microglia and cause pro-inflammatory cytokine secretion, which may directly cause neuronal injury (see Fig2) [25]

Aβ accumulation activates the acute immune response of both microglia and astrocytes which are responsible for the production and the activation of inflammation-related proteins involved in cytokines, chemokines, ROS, cyclooxygenase (COX), nitric oxide (NO) and pro-inflammatory mediators [56]. This process is done through two steps. At the beginning, Aβ activates TLRs and RAGE receptors, which can activate NF-κ B and AP-1 transcription factors, induce the ROS production and the expression of inflammatory cytokines. Then, these inflammatory factors stimulate the astrocytes, which amplify the pro-inflammatory signals, inducing a neurotoxic effects [47]. In addition, previous studies have reported that NF-κB significantly controlled chemokine and adhesion molecules secretion in astrocytes, promoting peripheral lymphocyte infiltration, therefore increasing inflammatory response [28].

There is a clear link between Aβ generation, microglia activation and inflammation that results in neuronal apoptosis.

Several inflammatory cytokines as well as chemokines with the highest elevated levels of in the AD brain compared to the normal people are: interferon γ (IFN-γ) and tumor necrosis factor α (TNFα), interleukin 1β (IL-1β), and interleukin 6 (IL-6). IFN-γ and TNFα not

only have toxic effects on neurons but have also reduce levels of insulin degrading enzyme, a key Aβ degrading protease [19].This means part of clearance mechanism are broken, and in turn, boost Aβ aggregation. Moreover, TNFα and IFN-γ have been shown to increase the production of Aβ from APP expressing cortical neurons as well as disrupt the ability of microglial cells to degrade Aβ [30]. It also has been found that IL-1β enables to potentiate the cytotoxicity of Aβ in neuronal cell culture, as well as promote the release of NO from astrocytes [21]. NO is a kind of strongly active free radial gas, which reacts with oxygen ions to form nitrite oxide, and causes oxidative stress to make lipid peroxidation. Hence, leading to both neuronal apoptosis and clearance of amyloid and other neurotoxic products. IL-6 increases the overexpression of ADP, thus promote the formation of Aβ. Remarkably, overexpression of IL-1 and IL-6 in the brain results in extensive gliosis which may be beneficial in the disease process by stimulating increased amyloid phagocytosis rather than mediating a neurotoxic feedback loop [32]. Furthermore, the inflammatory mediators generated by resident CNS cells are shown in research that can induce the production of adhesion molecules and chemokines, which further triggers the inflammation. Finally, over-expression of COX doubles Aβ plaque formation, while reduction of prostaglandin signaling through the EP2 receptor is associated with reduced beta-secretase 1 (BACE) cleavage of APP into Aβ.

7.3 Tau hyperphosphorylation

Tau protein is a is a phosphoprotein that exhibits properties of heat resistance and high solubility.This protein is suggested to be effective for microtubule assembly that phosphorylation negatively regulates its ability to stimulate microtubule assembly [42]. Tau protein promotes the assembly and stability of microtubules, which transport necessary nutrients and molecules as well as transfer information from soma to synapse [45]. The aggregates of tau protein will cause the disruption of microtubules, thus results in neuronal death.

Many different experimental systems using both cell and animal models have shown that aggregated Aβ peptides may induce tau hyperphosphorylation both in vitro and in vivo, stabilize tau aggregates, and promote the propagation of new tau aggregates [68]. There are results established that changes in brain metabolism, such as increased release and phosphorylation of tau amino acid residues 217 and 181, can be caused by Aβ pathology induces a change in brain metabolism of tau during which phosphorylation at position 217 maybe a more pronounced early change [67]. Moreover, studies have established Aβ pathology first induces subtle changes in tau metabolism in dystrophic neurites surrounding the Aβ plaques, before many years of formation of widespread tangle pathology [58]. This could be proved by an recent work showing that in early stages of AD, Aβ deposition in humans leads to an increase in the CSF levels of tau proteins, especially P-tau217 and P-tau181. It is still unclear exactly how Aβ exerts its effects on tau. Several possibilities exist, including that Aβ may induce tau alterations through specific binding to receptors (or nonspecific binding to lipid membranes) [30]. Another possibility is that Aβ is linked to tau indirectly through changes in microglial or astrocytic activity, which in turn induces tau pathology [50]. Furthermore, it has been mentioned is that Aβ aggregates can cross-seed with tau proteins to propagate tau aggregation [32]. Besides, as Aβ triggers the oxidative stress which has been shown enables to induce tau hyperphosphorylation. This can be thought as an indirect way for Aβ to cause tau hyperphosphorylation through activation of Gsk3β and Cdk5. Furthermore, one recent finding from a study of a rare APOE variant demonstrated that a binding of proteins to heparan sulfate proteoglycans may mediate the relationship between Aβ pathology and tau aggregation. Some scientists has reported that oligomeric Aβ specifically exacerbates protopathic seeding by tau [59].

7.4 Cholinergic neurons

In the AD, there is a severe reduction of in the basal forebrain as well medial septal region (medial septum and diagonal band of Broca, MS/DB). Even though various neurotransmitters containing cell bodies and axonal terminals in end-stage AD have shown a general decline, the most consistent losses are seen in the cortical projections of BFCNs (basal forebrain cholinergic neurons). These are the main causes of memory and cognitive dysfunction in AD patients.

A wealth of data has pointed that the activation of BFCNs and the consequent release of ACh(acetylcholine) which is a neurotransmitter in CNS, in the cortex mediate cognitive processes, including attention and memory. In the case of AD, Aβ activated GSK-3β,results in the phosphorylation of tau protein and mitochondrial pyruvate dehydrogenase [64]. This leads to the reduction of activity of enzymes, thus a low level of pyruvate dehydrogenase converts into acetyl coenzyme A, results in the synthesis of ACh decrease. This creates barriers to neurotransmitter delivery and declines activity of cholinergic system. In turn, the decrease in ACh promotes the formation of Aβ, creating a vicious cycle. On the other hand, research has suggested that while Aβ42 and Aβ oligomeric species accumulate in BFCNs work together with increased levels of C99, they devotes to the dysregulation of early endosomes. Then, dysregulation of endosomes reduces axonal transport of NGF/TrkA(tropomyosin-related kinase) signaling endosomes, containing Rab5-positive signaling [46].

Additionally, decreased retrograde transport of NGF signals related to BFCNs dysfunction as well. Thus, continuing compromise of retrograde axonal transport of NGF/TrkA signaling endosomes severely compromises the trophic status of BFCNs with marked changes in cell bodies and further shrinkage of axonal arbors and synaptic dysfunction [57]. However, the pathway Aβ within endosomes used to induce activation of Rab5 is unknown. Furthermore, it has been reported tau-mediated toxic event include compromised transport of TrkA may be related to the compromising of trophic support of BFCNs in addition to Aβ toxicity.

Nevertheless, since Aβ is the main culprit mediating dysregulation of tau homeostasis, the damage caused by tau protein can also be thought to be indirectly induced by Aβ. Some work suggested Aβ impacts processing of APP within endosomes, for example by compromising the activity of γ-secretase, this would lead to increased levels of C99 which enables to work with Aβ causing disruptions. Last, sustained microglial activation which induced by Aβ results in defective Aβ phagocytosis and release of pro-inflammatory cytokines. The cumulative effect of this also atrophy and eventual death of BFCNs [98]. Moreover, a recent research about rats found that accumulation of Aβ oligomers specifically interfere with presynaptic cholinergic mechanisms in the cortex by primarily disrupting choline uptake mechanisms [39]. To conclude, toxic Aβ and tau oligomers triggered various reactions to progressive compromise of retrograde NGF signaling, increasing deficits in synaptic function, and dysregulation of secretion of NGF from postsynaptic targets and activation of nearby microglia, to eventual demise of BFCNs. Another area that needs to be mentioned is that excitotoxicity triggered by Aβ-induced septal glutamatergic neuronal damage may contribute to MS/DB cholinergic neuronal degeneration according to research contributes to the development of AD.

7.5 Neuronal Apoptosis

Recent studies have shown that in AD brains and in cultures of neurons exposed to Aβ, the dying cells display the characteristics of apoptosis.

Aβ accumulation interacts and cross-links with transmembrane receptors like APP and secretion pathways. This leads to inhibition and abnormal activation of signaling routes, thereby triggering apoptosis. Specifically, previous studies have proved that amyloid fibrils can result in mechanical damage of the cell membranes by interacting with them through exposed hydrophobic surfaces, leading to disruption of the ion homeostasis and necrosis, as well physically damage of cells [100]. Small Aβ oligomers can bind to membrane receptors and penetrate cells where they disrupt function of the cellular systems, causing an unregulated influx of calcium ions into the cytosol from the surroundings and the endoplasmic reticulum of the cell through disrupted membranes. Since calcium is a main mediator of cell death that leads to neuronal apoptosis by releasing mitochondrial Cyt-c(cytochrome c) and activation of the caspase system, Aβ oligomers eventually triggers apoptosis, meaning that calcium in turn stabilizes Aβ oligomers.

It has also been demonstrated in cultured neurons that Aβ induces the Ca2+-dependent activation of calpain I. Calpain I has a function of cleaving p35 which is the regulatory subunit of cdk5, to p25, in consequence leading to constitutive cdk5 activation [58]. Because p25 and cdk5 overexpression results in the apoptosis of cultured neurons, it is likely that one-way Aβ induces cell death is through the activation of p25 and cdk5.

In addition, studies have also proved that a critical concentration of Aβ inhibits protein arginylation by Ate1, leading to the stabilization of misfolded and toxic proteins, including pro-apoptotic protein fragments. And subsequent suppressing protein degradation through the Arg/N-end rule pathway that is a part of UPS(ubiquitin-proteasome system).Finally, inducing cellular apoptosis. Moreover, N-terminal arginylation mediated by Ate1 has been shown to activate autophagic adaptor p62/STQSM/Sequestosome-1, promoting autophagic flux and lysosomal degradation. Due to lysosome in the autophagy system and UPS are both primary structures responsible for clearance of Aβ, hence damage to cells and eventually apoptosis happened as a result of dysfunction of them. Considering in this aspect, Aβ triggers a decline in protein arginylation following impairment of Ate1 activity may indirectly affect a wide array of cellular processes, like the dysfunction of UPS and autophagic lysosomes, thus causing neuronal apoptosis [63].

As mentioned above in this review, excitotoxicity promotes the death of both cholinergic and glutamate neurons. This is owing to Aβ can overstimulate NMDAR (N-methyl- D-aspartate receptor) to trigger excitotoxicity. Virtually, toxicity induced by excessive activation of NMDAR is considered as the core mechanism of Aβ-triggered neuronal damage. Further evidence supporting the role of NMDAR in toxicity of Aβ is that memantine, an uncompetitive NMDRA antagonist, has been demonstrated to protect against Aβ1–40- induced MS/DB neuronal damage in a recent experiment ,thus it enables to improve both cognitive and behavioral symptoms of AD.

The last point named here is that Aβ is able to induce neuronal apoptosis through the mitochondrial pathway. Since ROS acts an important role in apoptosis induction under both physiologic and pathologic conditions. Large evidences have illustrated that direct or indirect ROS action mediates mitochondria to release Cyt-c and the release of Cyt-c subsequently triggers caspase activation. While Aβ in charge of the increased production of ROS.

8 Conclusion

It is known that AD is the most prevalent neurodegenerative disease, especially in the elderly population. Although research in recent decades has attempted to identify the main cause of this neurodegenerative disease, the pathogenesis of AD remains unknown.

One thing that is clear is that the pathogenesis of AD is the result of the interaction of multiple factors. Currently, the pathogenesis of AD is mainly studied in the following aspects: amyloid cascade hypothesis, tau hyperphosphatation, effect of GSK-3β, and cholinergic injury hypothesis. There is no doubt that the pathogenesis of AD is more favorable to the amyloid cascade hypothesis, as Aβ plays a key role in the development of AD and it is involved in the interaction of these various mechanism. As can be seen from this review, many research have been done to identify the cause of Aβ's appearance as well as accumulation, and which form(s) are mainly responsible for neurotoxicity and how they trigger neuronal apoptosis. Numerous researches reveal

the complex mechanism by which Aβ induce AD, based on its neurotoxicity, allowing it to be related to a range of reactions including oxidative stress, inflammation, tau hyperphosphatation, cholinergic neuron damage as well neuronal apoptosis(Some of the derived mechanisms may not be mentioned in this review). It is believed that complicated linkages existed among the mechanisms, which may lead to a series of vicious cycles, in addition to the cycles inherent in each mechanisms like Aβ-induced harmful reactions in turn promote the production of Aβ and thus exacerbate the adverse effects, as detailed earlier in the review. Hence, the current research on Aβ has gone from focusing on its roles in every single domain to seeking the potential connections among different mechanisms and how they interact with each other. Scientists are also trying hard to figure out which response is the first to trigger by Aβ, that subsequent radiation other aspects. In general, the mechanisms of Aβ causing AD are still have many problems need to be explored, but it has been widely accepted as the initial motivation of AD. Massive targets have been identified for inhibition, clearance and initiation of AD by Aβ. Moreover, a large number of related drugs have been developed to treat AD. However, so far there has yet been a satisfactory therapeutic developed to combat AD and none of these drugs stopped patient's symptoms from getting serious. Drug failures and erratic results in clinical trails, boosted experts in this field to think deeply about the future of Aβ-specific treatments. One fresh viewpoint considered Aβ should be regard as an important biomarker for diagnosing AD severity in time, rather than a chief target for the AD treatment.

As a natural aging disease, AD is bound to be a multi-factor pathogenesis. Therefore, satisfactory conclusions are unlikely to be achieved with single method merely. Researchers still need to discover new breakthroughs via a large amount of further research on its mechanism. A more comprehensive thinking, starting from several emerging directions furthermore conducting researches through blending and interworking, has the probability of bringing unexpected gains.

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