

# Research Progress in the Pathogenesis of Alzheimer's Disease

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## Abstract

**Objective:** Alzheimer's disease (AD) is a kind of chronic degenerative disease of the central nervous system, characteristics of cognitive dysfunction, and behavioral disability. The pathological changes include the formation of senile plaques-containing beta-amyloid (A $\beta$ ), neurofibrillary tangles (NFTs), loss of neurons, and synapses. So far, the pathogenesis of AD is still unclear. This study was aimed to review the major pathogenesis of AD-related to the published AD studies in recent 20 years.

**Data Sources:** The author retrieved information from the PubMed database up to January 2018, using various search terms and their combinations, including AD, A $\beta$ , NFTs, pathogenesis, and genetic mutation.

**Study Selection:** The author included data from peer-reviewed journals printed in English and Chinese on pathophysiological factors in AD. He organized these informations to explain the possible pathogenesis in AD.

**Results:** There are many amounts of data supporting the view that AD pathogenesis so far there mainly are A $\beta$  toxicity, tau protein, gene mutation, synaptic damages, intermediate neurons and network abnormalities, changes in mitochondrial function, chemokines, etc., Its nosogenesis may be involved in multiple theories and involved in multiple molecular signaling pathways, including A $\beta$ , tau protein, and synaptic anomaly; mutual relationship between the mechanisms urge jointly neuronal degeneration.

**Conclusions:** This review highlights the research advances in the pathogenesis of AD. Future research has needed to fully disclose the association between multiple pathogenesis at the same time to interdict multiple signaling pathways, etc.

**Key words:** Alzheimer's Disease; Beta-Amyloid; Neurofibrillary Tangles; Pathogenesis

## INTRODUCTION

Alzheimer's disease (AD) is a kind of chronic degenerative lesion of the central nervous system (CNS), taking place in presenium and senium. AD is the most common dementia form in one's age. The pathogenesis of AD is as yet unclear entirely. It is stated that AD is a complicated heterogeneous disease, its attack related to the involvement of multiple factors, including heredity factors, neurotransmitter, immune factors, and environmental factors. At present, there are mainly beta-amyloid (A $\beta$ ) theory, tau protein theory, nerve, and blood vessel theory are some of these in the aspect of the interpretation to the nosogenesis of AD. With the constant depth of the researches to AD, many theories were raised such as oxidative stress, inflammatory mechanism, mitochondrial dysfunction, and autophagy, providing a broader way of thinking for us to invest more in cognition to AD.

## GENETIC MUTATION

According to whether there is a family history, AD is divided into familial AD and sporadic AD (SAD). In AD, amyloid precursor protein (APP) and presenilin (PS) are already the definitive virulence genes.<sup>[1]</sup> For SAD >90% of AD, major influencing genes include apolipoprotein E (ApoE) gene, clusterin gene, complement receptor 1 gene, and phospholipids bind to clathrin protein (PICALM) gene.<sup>[2]</sup> Along with the development of genetic research into AD, more new genetic loci for AD have been discovered, including cholesterol metabolism gene (CH25H, ABCAL,

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and CH24H),<sup>[3]</sup> Sterol O-acyltransferase (Soat1) and prostaglandin-endoperoxide synthase 2 (Pgs2)<sup>[4]</sup> genes, and angiotensin-converting enzyme gene<sup>[5]</sup> are some of these. Researches in recent years have shown that microRNA (miRNA) was closely related to the nosogenesis of AD, miRNA playing an important role in AD and gene translation expression.<sup>[6]</sup> The study by Li *et al.*<sup>[7]</sup> have found that ApoE4 gene appears frequently in the cases of the advanced AD patients and that ApoE4 is the risk factor of AD occurrence, the frequent occurrence rate of ApoE4 gene positively related to the probability of AD. Studies have found that SLC25A38 protein was closely bound up with neurodegeneration and nerve cell apoptosis, the protein being the material support required for mitochondria to work normally. If SLC26A38 gene mutates, its functional damage can result in imbalances in the brain, inducing the CNS disorders.<sup>[8]</sup>

## BETA-AMYLOID

A $\beta$  is produced by neuron, passing into the blood and cerebrospinal fluid (CSF), and A $\beta$  would not deposit physiologically due to the organismic clearance mechanism for A $\beta$ . Even so, accumulational soluble A $\beta$  oligomer can damage synaptic junction and generate neurovirulence.<sup>[9]</sup> In pathology situation, the unbalance between the production and clearance rate of A $\beta$  can lead to its sedimentation, causing for AD to happen using tau protein poisonousness, destroying intracellular calcium homeostasis and cholinergic nerve system, inducing neurofibrillary tangles (NFTs), etc., Hence reducing A $\beta$  deposition can improve AD of a large extent and make it possible the targeted therapy of AD in allusion to A $\beta$ , such as A $\beta$  antibody and beta-secretase cleaving enzyme (BACE) inhibitor. Recent studies show that A $\beta$  sedimentation can be reduced illuminating mice by 40 Hz LED lamp.<sup>[10]</sup> However contrary to what is always believed that A $\beta$  oligomers have cytotoxicity, there is research<sup>[11]</sup> finding that A $\beta$  oligomerization can have also protective effect and confront the infection of microorganisms and worms in the body. Moreover, research<sup>[12]</sup> showed that there is suspected-non-AD pathophysiology, the patient having neural degeneration but being not found A $\beta$  sedimentation, this suggests that the production of AD cannot always accompany A $\beta$  sedimentation. Recent neuroimaging and neuropathology researches revealed that A $\beta$  sedimentation was mainly related to cognitive disorder of the old,<sup>[13]</sup> and it is not very relevant with other clinical features.

## THE ABNORMAL AGGREGATION OF TAU PROTEIN

Tau protein is chiefly distributed in neures, its repetitive elements Pro-Gly-Gly-Gly helping it bind to microtubulin, get together microtubule, and maintain the stability of microtubules, which plays an important part in keeping the integrity of cytoskeleton and axonal transport.<sup>[14]</sup> NFTs are the important pathological marker of AD, to formed gather by hyperphosphorylated tau protein and paired helical filament. The reason of tau hyperphosphorylation is the

increased protein kinase activity, protein kinase activity such as glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) activity can be decreased to reduce phosphorylation, and decreased phosphatase activity is the one reason hyperphosphorylation. In addition, the lack of glucose in the brain can make tau hyperphosphorylated by mediating the signal pathway of p38 mitogen-activated protein kinase (MAPK), increasing the level of glucose in the brain may provide a new idea for treating AD.<sup>[15]</sup> Research<sup>[16]</sup> has shown that colorless methylene blue (LMTM), tau protein inhibitor, did not effectively improve the cognitive impairment of the mild-to-moderate AD patients, and the three phase of the clinical trial of the drug LMTM ended in failure. However, the immune clearance therapy directed against AD does not necessarily fail, and immunotherapy will have brought prospect, on account of plentiful preclinical data and emerging clinical data. Tau protein may be able to diffuse from a brain cell to another brain cell, suggesting that the diffusion of tau among cells is prevented passed could by the antibody of blocking tau protein.<sup>[17]</sup> In the model of tau-P301L transgenic mouse, immunization therapy can facilitate the defense reaction of microglial cell, accelerate the clearing to tau protein, and protect nerve cell from the toxic effect induced by tau.<sup>[18]</sup> Research<sup>[19]</sup> challenges the neurotoxic effects of tau phosphorylation in AD nosogenesis and the research found that at least in the early stage of AD, phosphorylation of characteristic sites in tau protein was able to inhibit the toxicity of A $\beta$ , being that tau phosphorylation-mediated by p38MAPK can antagonize the postsynaptic excitation toxicity caused by A $\beta$ . Accordingly in the AD model mice, the consumption of p38MAPK-mediated phosphorylated tau maybe bring about neural degeneration and cognitive obstacles, then the increase of phosphorylated tau can remove these changes.

## SYNAPTIC DAMAGES

A large number of studies have found confirmation that the key characters of AD are fewer synapses and changes in synaptic plasticity, and the degree of synaptic decline of specific location such as hippocampus has the best relevance with the cognitive decline in AD patients, long-term potentiation (LTP) learning and memory playing a vital role. Synaptic plasticity and LTP are all about N-methyl-D-aspartate receptor (NMDAR), A $\beta$  oligomer facilitates astrocytes (AS) to release glutamate by a7nAChR and activates NMDAR, making ERK signaling pathway to be suppressed and finally suppressing LTP,<sup>[20]</sup> therefore the synaptic damages caused by NMDAR hyperactivation are the possible mechanisms of AD occurring. Meanwhile, it was ago taken for that synaptic loss was the secondary change of protein denaturation, but the research of Hong *et al.*<sup>[21]</sup> found that at the beginning of the AD cynapses could be already reduced and the decrease maybe is anterior to the formation of plaques, but from the abnormal of synaptic pruning mechanism during normal brain development. Contemporary, they also found that cynapses can be

protected by inhibiting the high expression protein C1q participating in normal synaptic pruning, and C1q can be in view as drug target. Current research<sup>[22]</sup> has found that in baboon brain the synaptic number may be detected using radioligand C-UCB-J with landmark synaptic vesicle glycoprotein 2A (SV2A) targeted combination, being SV2A-positron emission tomography imaging method, and the using of this non-invasive way has a lot of promise in living humans.

## INTERMEDIATE NEURONS AND NETWORK ABNORMALITIES

Study and memory of AD patients are severely damaged, in the learning and memory formation process, neuronal activity can change, inducing synaptic reconstruction and ultimately prompting to reconnect the network of neurons. A $\beta$  deposition, synaptic loss, tau protein phosphorylation, and cholinergic system disorders will bring about the neuronal injury. The loss of intermediate neurons will happen at the time of progress AD, and intermediate neurons play an important regulatory role to the excitability and synchrony of hippocampal neural networks. It is all the time deemed that synaptic loss and abnormal structural reconstruction take place around A $\beta$  plaque,<sup>[23]</sup> also the neuronal hyperactivity round A $\beta$  plaque. Inhibitory neurons of parvalbumin (PV) and somatostatin (SOM)-position are important intermediate neurons in the hippocampus participating in learning and memorizing,<sup>[24]</sup> and AD-like pathologic change is able generated by insufficiency of O-LM intermediate neurons (an SOM intermediate neuron).<sup>[25]</sup> In the model of mouse transgenic CRND8, researchers found that intermediate neurons had changed before A $\beta$  aggregates in the earlier stages of AD, i.e. ahead of AD clinical presentations, and falling in numbers of neuropeptide Y and PV-immunocompetent (PV-IR) cell in the hippocampus, proving for the first time that intermediate neurons in the hippocampus associated with AD actually changed in model mice at a month old, and these functional lesions anterior to A $\beta$  sedimentation maybe lead to cognitive impairments in AD.<sup>[26]</sup>

## CHANGES IN MITOCHONDRIAL FUNCTION

Neurons are the cells highly dependent on mitochondrial oxidative phosphorylation of energy. Therefore, changes in mitochondrial function are closely related to the age-related occurrence of AD. Compared with young mice (4-month-old), in senile mice (24-month-old) the levels of 5-hydroxymethylcytosine (5hmC) and mitochondria DNA methyltransferases1 expression lowered in the mitochondria of the prefrontal cortex, but the expression level of mitochondrial coding genes increased, whereas the levels of 10–11 translocation methylcytosine dioxygenase 1 (TET1)~TET3 were not affected, revealing for the changes of mtDNA methylation pattern with age may to participate in the body's adaptive mechanism for aging.<sup>[27]</sup> There

are differences for DNA methylation level in the discrete brain areas of AD patients, and studies on the methylation of the whole genome in the hippocampus of early and late AD patients indicated that the expression levels of 5-methylcytosine (5mC), 5hmC and TET1 increased, but the levels of 5-formylcytosine and 5-carboxylcytosine markedly decreased, to suggest for changes in the methylation and demethylation patterns of the whole gene to be pathologic changes of AD occurring early in life and before clinical phenotypes of AD patients.<sup>[28]</sup> The classic CpG site and noncpg site 5mC levels in the mtDNA D-loop area of the cerebral cortex mtDNA markedly increased, the extent of increase proportional to the stages and severity of the disease, and the 5mC level of mitochondrial NADH dehydrogenase subunit1 gene increased slightly, along with upregulation of the gene expression, suggesting the modification of methylation pattern of mtDNA D-loop area and coding gene results in likely AD occurring and changes in clinical symptoms.<sup>[29]</sup> Although there are many miRNAs participate in multiple expression regulations-mediated AD pathology changes genes as  $\beta$  site APP-cleaving enzyme 1 (BACE1) etc., resulting in the occurrence and development of AD. However, it is not reported yet to study the relation of mitochondrial miRNAs with pathological changes and clinical manifestations of AD, but it is going on and on that the research about interaction and mechanism for two.<sup>[30,31]</sup>

## CHEMOKINES

Chemokines play pleiotropic roles in the pathology of AD, a chronic inflammatory disease of CNS. The neuropathological features of AD include NFTs, amyloid plaques, neuroinflammation, and neuronal synaptic loss. Chemokines are involved in the pathogenesis of AD by activating or regulating inflammatory cells or glial cells, playing dual key roles of the pro-inflammatory and anti-inflammatory properties in AD. The levels of chemokines in serum, cerebrospinal fluid, and brain tissue of AD patients are changed accordingly.<sup>[32]</sup>

## MICRORNA-137

miRNA is endogenous noncoding small molecule RNA and can involve in regulating the development and function of nervous system.<sup>[33]</sup> miR-137 (or miRNA-137) as a member of miRNA takes part in pathogenetic process of a variety of neurological diseases including AD.<sup>[34]</sup> However, now it is not entirely clear to specific molecular mechanism of miR-137 taking part in the occurrence and development of AD. miR-137 is to delay the onset of AD primarily through inhibiting extracellular A $\beta$  sedimentation, regulating and controlling calcium homeostasis and correcting tau protein hyperphosphorylation, its function coming true primarily through the following routes: (1) the level of serine palmitoyltransferase (SPT) is up-regulated up-regulating serine palmitoyltransferase long chain 1 (SPTLC1) expression by posttranscriptional regulation. Because that SPT can promote the formation of ceramides and that ceramides are

not just about the endogenous generation and synthesis can also cause oxidative stress-mediated neuronal death, miR-137 decrease A $\beta$  endogenous generation, and resynthesis available through posttranscriptional regulation of SPTLC1, then playing the role of delaying neuronal death.<sup>[35-39]</sup> (2) miR-137 inhibits calcium homeostasis imbalance caused by CaV1.2 (calcium channel, voltage-dependent, L type, and  $\alpha$ 1C subunit) overexpression and error positioning on the axon of tau protein created by CaV1.2 and calcium ion by regulating the CaV1.2 expressed by downstream target gene CACNALC (calcium voltage-gated channel subunit  $\alpha$  C).<sup>[40-49]</sup> (3) miR-137 regulates cadherin expressed the downstream target gene of calcium mucin (CDH) gene, and under the action of old protein 1 (PS1) cadherin combines with phosphatidylinositol 3-kinase (PI3K) and inhibits tau protein phosphorylation can by PI3K/Akt/GSK-3 pathway, thus to inhibit neuronal death.<sup>[50,51]</sup>

The root is based on the pretest of life information, miR-137 still exists other potential AD-related target genes, as SMEK, HMGN3, DR1NA, DMRT3, MBNL2, and KCNMB2, but these target genes have at present less research about molecular mechanism in AD pathogenesis.

## NEUROINFLAMMATION

AD patients and animal models exhibit the overactivation of microglia (MG) and AS, causing neuroinflammation, leading to neuron death. Inhibition of MG activity can alleviate A $\beta$  plaques. A growing number of studies have found that neuroinflammation is involved in the development and progression of AD. MGs are highly specialized histological macrophages in CNS, similar to the peripheral mononuclear phagocytic system in function and origin.<sup>[52]</sup> Megalophages differentiate into two types of antagonistic phenotypes in the immune response: the M1 phenotype that causes tissue damage and the M2 phenotype that promotes tissue repair.<sup>[53]</sup> MG's role of inflammation in AD is similar to the previous statement.<sup>[54]</sup> MG in the circumference of A $\beta$  plaques is M1 phenotype and was activated as inflammatory or nerve toxicity phenotype under the action of miR-689, miR-124 and miR-155,<sup>[55]</sup> meanwhile to inhibit MG to the M2 phenotype. M1MG has the weak phagocytic effect of A $\beta$ , can at the same time induce degeneration of the nervous system, and aggravate nerve injury. Generally speaking the scavenging action to A $\beta$  of the M1 type to tissue damage lowered, accentuated A $\beta$  deposition, and participated in cerebral tissue damage of AD patient.

In AD, activation and atrophy of AS exist simultaneously. In mouse model of early-stage AD, AS represents in form as atrophy, decreased dendritic branching and volume contraction, and effects the synaptic formation of endothelium and other parts, thus leading to the cognitive function of AD patients to deteriorate.<sup>[56-58]</sup> Early stage AD, AS is activated and release gliotransmitters, interacted with neurons. When advanced AD, glial fibrillary acidic protein (GFAP)-positive AS are mainly related with senile

plaques and A beta deposition around the blood vessels. Inhibiting expression of GFAP in AD mouse brain tissue makes the neural support of AS decreased.<sup>[59]</sup> AD anaphasis, GFAP expression augment is not clearly correlated with A $\beta$  deposition. A $\beta$  swallowed by AS is stored in the cell, forms A $\beta$  fragment of virulence, and leads to lysosomal function inactivation, releasing A $\beta$  fragment by the way of exocytosis into brain tissue, thereby inducing apoptosis of cerebral cortex neurons.<sup>[60]</sup> Extracellular accumulated A $\beta$  induces the activation of AS, activated AS in the brain of AD mouse mainly distributed in the hippocampal area, the inner smell and the prefrontal cortex,<sup>[56]</sup> this discovery consistent with the inner olfactory cortex and the prefrontal cortex mostly easily injured by AD. Immunoreactive AS of mice brain tissue increase markedly mathematically. A $\beta$  deposition is mainly related to casein kinase 2-immunoreactive AS. Inhibiting selectively CK-2 expression by CX-4945 (Silmitasertib), the secretions dropped obviously of interleukin-1 (IL-1), monocyte chemotactic protein-1, and IL-6.<sup>[57]</sup>

## CELL AUTOPHAGY

Autophagy is the major cell metabolic pathways for biodegradation of macrobiotic proteins and cytoplasmic organelles, decontaminating self-redundant or injured organelles. Recent studies showed that autophagy maybe participated in the pathogenesis of neurodegenerative diseases, as AD etc. Normally autophagy possesses neuroprotective effect. When the autophagy function is blocked, degradation, and removal of obstacles to A $\beta$  caused deposition and neuron damage, resulting in AD occurrence. A $\beta$  deposit before, it has been found that a large number of autophagy bodies exist in PS1/APP mouse neurons, neuronal number of autophagic vesicles in 8 weeks old mice five times higher than normal mice, 9 months old mice at least 23 times higher.<sup>[61]</sup> Gene expression technique suggested that in AD patient brain tissue, Beclin1 mRNA expression was decreased, Beclin1 hypoproteinemia and mature autophagy formation obstacle, leading to autophagic vesicles concentrated, and A $\beta$  increased formation.<sup>[62]</sup> Autophagic inhibitor might more activate  $\gamma$ -secretase more than inductor and promote A $\beta$  production and accumulation, but have no impact on eliminating A $\beta$ .<sup>[63]</sup>

Autophagy possessed a scavenging action to tau protein aggregation, and autophagy defects might cause tau protein removal disorder. Hence, tau protein hyperphosphorylation or polymerization in neurons of AD patients formed NFTs. On the basis of starvation-induced autophagy the degradation of tau and phosphorylation tau in two mice embryonic fibroblasts cells was observed, the results showed that the degradation rate of tau and phosphorylated tau was significantly reduced in the cells with autophagy lack, suggested that autophagy can promote the degradation of tau and phosphorylated tau, and autophagy inhibition may increase the cytotoxicity of tau.<sup>[64]</sup> In AD patient brain tissue, a large collection of organelles in the nervous and swollen axons of a nutritional disorder means the axon

transport anomaly.<sup>[65]</sup> To inhibit neuronal autophagy makes the abnormal structure of axon terminal membrane with severe axon edema, it is inferred that autophagy is a key mechanism for reconstructing and extending. When AD happens, mature autophagy and its reverse transport occurred with obstacles, leading to a large accumulation of autophagy intermediates (autophagic vacuoles) of neurotrophic and degeneration axons. Enhanced autophagy reaction and A $\beta$  removal defect of autophagy cavitation lead to the accumulation of A $\beta$  in AD.<sup>[66]</sup> Early phosphorylation of tau protein causes a defect in axon transport, resulting in the accumulation of autophagy vesicles and the inflammatory changes of the nervous protuberance could being the change of axonal reactivity resulted by abnormal aggregation of amyloid plaques, but cannot removing these abnormal clumps of proteins and damaging itself, ultimately unable to function transport effectively and affected the mature and normal function of autophagy.<sup>[67]</sup>

## ENDOPLASMIC RETICULUM STRESS FUNCTION

Influenced by genes, environment, age, etc., endoplasmic reticulum misfolded protein increased in AD neurons and homeostasis imbalance, caused endoplasmic reticulum stress (ERS),<sup>[68]</sup> playing an important role in the pathogenesis of AD and the apoptosis of nerve cells. The AD neuron ERS activated can cause a series of morphological functions of nerve cells, as calcium homeostasis changes and peroxide increasing, and can also activate unfolded protein response (UPR), to cause the expression of a series of apoptotic signaling molecules downstream. The final result of these reactions facilitates the apoptosis of nerve cells, causes a loss of neurons in the brain, cognitive dysfunction and increases AD. Moreover, ERS is also involved in the formation of A $\beta$  and abnormal phosphorylation of tau protein and promotes AD pathogenesis. To study the function of ERS in neurons is significant in understanding the pathogenesis of A D and treatment of A D. In ERS, eukaryotic initiation factor 2' phosphorylation increases the B site APP shearing enzyme (BACE) and prompts A $\beta$  generation. Expression activation of c-Jun N-terminal kinase-mediated by apoptosis signal-regulating kinase 1 could regulate APP shear-induced A $\beta$  intracellular accumulation, tau protein phosphorylation and trigger NFTs.<sup>[69]</sup> There is a lot of PS in mitochondria-associated ER-membrane (MAM), it is a component of the secretase. Therefore, changes in MAM functionality caused by ERS may also lead to A $\beta$  production.<sup>[70]</sup> A $\beta$  secretion may be also related to damage of activating transcription factor 6 (ATF6) in ERS. ERS expresses more high ER-associated DNA J protein 3 (ERdj3) could via the activation of unfolded protein response (UPR) ATF6 pathway. ERdj3 can be secreted one side to outside cell and combine extracellular dislocation protein to make it degraded and prevent its deposition; ERdj3 might play the role of its molecular partners on the other hand, binding to the mixins in ER and secreted outside cell to make fault fold proteins return to normal or degraded. Genereux *et al.*,<sup>[69]</sup>

studied the inhibiting effect of ERdj3 to A $\beta$ <sub>1-40</sub> deposition. They discovered when *escherichia coli* rer DJ3 (RERdj3) concentration for 370 nM (ERdj3: A $\beta$ <sub>1-40</sub> = 1:27), RERdj3 can suppress completely A $\beta$ <sub>1-40</sub> deposition; while bovine serum protein (inhibiting moderately A $\beta$  deposition) at the same concentration has less impact on inhibition of A $\beta$ <sub>1-40</sub> sedimentation. Therefore in AD, ATF6 pathway in ERS is injured may due to PS mutation making ERdj3 secretion drop and causes intracellular misfolding soluble A $\beta$  secreted outside cell, aggregating to form a soluble low polymer and amyloid fiber with protein toxicity, also deposited on the surface of the neuron and destructing function of neurons even to lead to its apoptosis.<sup>[71]</sup> Abnormal phosphorylation of tau protein is also about ERS. Found in AD brain neurons, phosphor- protein kinase-like endoplasmic reticulum kinase (p-PERK) was with GSK-3 $\beta$  together,<sup>[72]</sup> and p-PERK can make GSK-3 $\beta$  activity increased. GSK-3 $\beta$  is a protein kinase and it can promote tau protein phosphorylated. In human body neuroblastoma cell line (SH-SY5Y) cell, thapsigargin can stimulate tau protein phosphorylated,<sup>[73]</sup> found in basal cultured nerve cells in ERS tau protein degradation rate decreased and endogenous tau protein increased.<sup>[74,75]</sup>

## CONCLUSION

About AD pathogenesis, so far there mainly are A $\beta$  toxicity theory, tau protein, gene mutation, synaptic damages, intermediate neurons and network abnormalities, changes in mitochondrial function, chemokines, etc. Its nosogenesis may be involved to multiple theories, thus it can be seen that AD pathogenesis is very complicated, involved multiple molecular signaling pathways, including A $\beta$ , tau protein, and synaptic anomaly, etc.; the mutual relationship between the mechanism urges jointly neuronal degeneration. Future research has needed to fully disclose the association between multiple pathogenesis at the same time to interdict multiple signaling pathways and so on. For the moment research to AD prophylaxis and treatment is still a work in progress.

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## Conflicts of interest

There are no conflicts of interest.

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# 阿尔茨海默病机制的研究进展

## 摘要

**目的：**阿尔茨海默病（AD）是一种慢性中枢神经系统的退行性疾病，其特征是认知障碍和行为无能。其病理改变包括：老年斑的形成、神经原纤维缠结、神经元和突触丧失等。至今AD的发生机制仍不很清楚。该文旨在对近20年已发表的有关AD主要发生机制的研究做一综述。

**资料来源：**本人通过PubMed等数据库检索了截止到2018年1月的大量信息，使用了各种检索词和其组合如AD、A $\beta$ 、神经原纤维缠结、发生机制和基因突变等。

**资料选择：**本人列入了许多来源于以中、英文发表于同行评议杂志上的有关AD病理生理因素的资料。

**结果：**许多资料表明，迄今为止AD的发生主要与A $\beta$ 毒性、tau蛋白、基因突变、突触损伤等有关。AD的发生机制可能涉及多种理论，包含了多条分子信号通路如A $\beta$ 、tau蛋白和突触异常等；这些机制的相互作用共同促进了神经元的退变。

**结论：**该综述强调了近年来有关AD发生机制的研究进展。未来的研究应该在阻断多条信号通路的同时充分揭示AD多种发生机制间关系。