Screening of treatment targets for Alzheimer's disease from the molecular mechanisms of impairment by β -amyloid aggregation and tau hyperphosphorylation

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Abstract: β -Amyloid ($A\beta$) over-expression and tau hyperphosphorylation are considered to be the central events in the pathogenesis of Alzheimer's disease (AD). Studies on them may help elucidate the precise molecular pathogenesis of AD. Until now, although tau protein and $A\beta$ remain the foci of AD research, the etiopathogenesis of AD and effective drugs for AD treatment are still largely unsolved. The present review was mainly focused on the molecular mechanism of $A\beta$ aggregation-related impairment and the pathways leading to tau hyperphosphorylation, based on which some promising therapeutic targets for AD were also proposed.

Keywords: Alzheimer's disease; $A\beta$ aggregation; tau hyperphosphorylation; treatment targets

1 An introduction of β -amyloid ($A\beta$) and tau protein

Alzheimer's disease (AD) is a primary neurodegenerative disorder in the central nervous system. It is pathologically characterized by neuronal cell death and accumulation of protein filaments including insoluble extracellular deposits of $A\beta$ and intracellular neurofibrillary tangles (NFTs) consisting of tau protein. $A\beta$ plays an important role in the pathogenesis of AD. Since the first identification of $A\beta$ as a hallmark of AD a quarter of century ago^[1], numerous studies have been conducted to illuminate the underlying mechanism of dementia. $A\beta$ is formed after sequential cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein with a large N-terminal ex-

tracellular tail.

As a microtubule-associated protein, tau protein is attached to microtubules that transport materials to the nerve terminals to construct the network in the brain. In AD patients, tau is found inside neurons in a mesh of proteins called NFTs caused by abnormal tau phosphorylation^[2]. The reduction of methylation of protein phosphatase 2A (PP2A), a kind of hydrolase, is suggested to contribute to the hyperphosphorylation^[3]. On the other hand, the abnormal activation of the tau protein kinase has been demonstrated to cause hyperphosphorylation and generate NFTs^[4]. In this review, the pathways implicated in tau- and $A\beta$ -induced neuron impairment, and the targets for preventing tau hyperphosphorylation and $A\beta$ aggregation were summarized.

2 Neuron impairment induced by $A\beta$

2.1 $A\beta$ leads to calcium influx into neurons The calcium hypothesis was proposed for the first time in 1994

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by Khachaturian, who postulated that sustained intracellular calcium disturbances lead to AD. Calcium is a vital element in neuronal excitability, synaptic plasticity and neurotoxicity. In the process of A β aggregation, Ca²⁺ influxes from the extracellular environment or is released from intracellular endoplasmic reticulum (ER) stores, resulting in Ca²⁺ overloading and impairment in neuronal functions^[5].

A β aggregation in the brain initially causes synaptic dysfunction and catalyzes calcium influx that causes dynamin-1 degradation and promotes calpain activity^[6]. Dynamin-1 is an important protein in the process of synaptic vesicle recycling, whereas calpain is a kind of Ca²⁺-dependent protease that can destroy the synaptic vesicle function. Calpastatin has been demonstrated to be an inhibitor of calpain^[7]. Therefore, it is proposed that increase in the expression of calpastatin may ameliorate AD symptoms. Moreover, Visinin-like protein (VILIP-1) belongs to the neuronal calcium sensor family of EF-hand Ca²⁺ binding protein. With the increase in calcium concentration, VILIP-1 will be activated to influence protein configuration on cell membrane, contributing to impairment in nicotinic acetylcholine receptor (nAChR) which is closely associated with synaptic plasticity^[8]. In all, A β aggregation initially causes the disruption of calcium homeostasis, leading to the dysfunctions of neurons.

2.2 A β causes synaptic dysfunction Cholinergic transmission is an essential event for the release of neurotransmitter and acetylcholine as well as the activation of postsynaptic receptor. In severe AD, levels of acetylcholinesterase (AChE) and choline acetyltransferase (ChAT) are decreased by as much as 90% compared with those in normal group^[9]. Chiba T and colleagues found that intracranial A β aggregation would induce cholinergic dysfunction by inactivating Janus kinase 2 (JAK2) as well as signal transducer and activator of transcription 3 (STAT3)^[10]. Besides, another study indicated that the cholinergic function deficit could be attributed to the reductions in cholinergic markers at the beginning of A β accumulation^[11]. Therefore, A β aggregation may cause the decrease in cholinergic marker expression through the inactivation of STAT3.

Moreover, glutamate uptake also plays an important role in mediating neuron transmission. Chin's group have found that A β affects glutamate uptake via alpha-4 beta-2 subtype of nAChRs^[12]. Thus, A β not only influences the cholinergic system but also affects the other systems related to neuron transmission which is important for maintaining cognition.

The signal pathway of mixed lineage kinase 3 (MLK3)-MAPK kinase 7 (MKK7)-c-jun N-terminal kinase 3 (JNK3) will be activated by A β deposit, which could impair cholinergic function^[13]. Sotthibundhu's research suggested that mice deficient in P75 neurotrophin receptor (P75^{NTR}), a well-known mediator of neuron death, exhibited less neuron loss following A β treatment, compared with P75^{NTR} wild-type mice^[14]. However, A β may also trigger cholinergic dysfunction by promoting aberrant neuritic sprouting. Therefore, A β aggregation not only affects the receptors on the membrane related to cholinergic function, but also affects the matrix environment to induce synaptic dysfunction.

2.3 A β influences the immune system in the brain The brain has an endogenous immune system consisting of immunocompetent cells such as microglia and astrocytes. White JA *et al.* reported that treatment of astrocytes with oligomeric A β could result in promotion of astrocyte-mediated inflammation and generation of pro-inflammatory molecules, such as interleukin (IL)-1 β and tumor necrosis factor (TNF)- α ^[15]. Giovannini MG *et al.* revealed for the first time that p38 mitogen-activated protein kinase (p38MAPK) played a pivotal role in microglia signal transduction pathways in immune response to A β deposit^[16]. However, Salminen A *et al.* found that A β activated immune response via pattern recognition receptors (PRRs)^[17]. The immune reactions in brain may be extensively triggered by A β accumulation to perform phagocytosis to protect neurons from damage, but this may also have harmful side effects and cause impairment in brain.

The toll-like receptors (TLRs) are important elements in immune response induced by A β accumulation^[18]. TLRs are the main molecules that initiate the innate immune response. Previous studies have demonstrated extensive

A β deposition in an AD mouse model homozygous for a destructive mutation of TLR-4^[19] or transgenic mice that are deficient in TLR-2^[20], compared with wild-type mice, and both of the 2 models secrete more chemokines and cytokines to trigger immune response, such as TNF- α , IL-1 β , IL-10 and IL-17. Nevertheless, Lotz M *et al.* suggested that A β enhanced the actions of TLR-2 and TLR-4 agonists but not TLR-9-induced inflammation in primary mouse microglial cell cultures^[21]. Further studies on TLR-9 as a target for alleviating AD symptoms were conducted by Scholtzova H *et al.*^[22]. When the innate immune system was stimulated via TLR-9, they found a 66% reduction in the cortical amyloid burden compared with that in non-stimulated AD mice^[22]. These studies strongly indicate that TLR signaling is the main mediator of A β aggregation-induced impairment in the brain.

2.4 Targets screened to prevent A β -induced impairment The drugs for AD treatment are mostly AChE inhibitors that prolong endogenous release of acetylcholine (ACh) to ameliorate the symptoms of AD. PMS777 was identified in 2007 as a new compound that inhibits AChE^[23]. However, little is known concerning how the

cholinergic function affects A β deposition in AD. Decreasing A β expression and eliminating A β aggregation are the main methods for reducing A β toxicity. The ideal targets have been screened to prevent impairment by A β aggregation (Table 1).

Some new drugs and compounds that can alleviate A β aggregation have been discovered to treat AD. Butyrylcholinesterase (BuChE) is important for A β aggregation, and has become a hot target in the area of AD research. The compound Cymserine has been found to be capable of reversibly inhibiting BuChE function. Luo HM *et al.* have found that gamma-schisandrin extracted from Chinese herb can reduce A β expression in M146L cells^[24]. Nobiletin, a polymethoxylated flavone from citrus peels, can improve memory impairment by enhancing cAMP/protein kinase signaling pathway^[25]. Meanwhile, the compounds extracted from Chinese herb have a high potential in providing effective drugs for AD. Tiantai No.1, Futokadsura Stem, Huang-Lian-Jie-Du, and Fuzhisan from Chinese herb have been found to improve AD symptoms^[26,27].

Based on the process of A β generation, the inhibitors of β -secretase and γ -secretase are preferred therapeutic

Table 1. The targets for drug discovery of Alzheimer's disease

Targets	Drug/ Compound	Brief mechanism
AChE	Tarcrine(approved)	Inhibiting AChE function
BuChE	Cymserine	Inhibiting BuChE function
MLK3	Undiscovered	Inhibiting MLK3 -JNK3 signal pathway
P38MAPK	Undiscovered	Inhibiting p38MAPK in immune response
TLRs-2,4	Undiscovered	Upregulating immune receptors
TLR-9	Undiscovered	Promoting TLR-9 action
α -Secretase	Nobiletin	Activating α -secretase to decrease Abeta load
NF-kappa B	Donepezil	Activating NF-kappa B and cAMP pathways
M1-type muscarinic receptor	Undiscovered	To be an antagonist for selective M1 receptor
NMDA receptor	Undiscovered	Regulating synaptic NMDAR responses
γ -Secretase	Undiscovered	Preventing Abeta over expression
LRP	Undiscovered	Increasing LRP expression for A β clearance
Calcium channel	Undiscovered	Stabilizing calcium homeostasis

AChE: acetylcholinesterase. BuChE: butyrylcholinesterase. MLK3: mixed lineage kinase-3. p38MAPK: p38 mitogen-activated protein kinase. TLR: Toll-like protein. LRP: lipoprotein receptor-related protein.

targets for reducing A β load in the brain. Developing the amyloid vaccine is a potential therapy to retain A β in the plasma, precluding its transport back into brain. The beneficial effects of the vaccine in cognitive protection have been reported in antibody responders^[28]. Although a clinical trial using active immunization with A β 1-42 was suspended because approximately 6% of patients in trial developed meningoencephalitis, a safe and effective oral vaccine using adeno-associated virus vector carrying A β cDNA has been reported^[29].

3 The pathways leading to tau hyperphosphorylation

3.1 Reduction in dephosphorylation of phosphorylated tau (p-tau) Tau is a microtubule-associated protein and is vital for neuron transmitting. NFT is a hallmark in AD brain. NFTs are composed of paired helical filaments (PHF) consisting of hyperphosphorylated tau protein. Recent studies have suggested that the protein phosphatases (PPs), PP1, PP2A, PP2B, and PP5, can dephosphorylate tau *in vitro* as well as *in vivo*^[30]. PP2A is the main enzyme that prevents hyperphosphorylation, and the activity of PP2A has been demonstrated to be reduced in the brain of AD patients^[31]. Besides, decreased PP2A mRNA expression has been detected in AD hippocampus^[32]. Furthermore, Chohan MO *et al.* found that tau hyperphosphorylation was observed when the inhibitor-2 of PP2A (I2PP2A) shifted from nucleus to cytoplasm, accompanied by cleavage of I2PP2A into a 20-kDa fragment^[33]. In the brain of AD patients, the dephosphorylation of p-tau by PP5 is shown to be decreased, resulting in tau hyperphosphorylation^[34]. In the research of Sun *et al.*, tau hyperphosphorylation was observed in mice treated with Calyculin A (a potent and specific inhibitor of PP1 and PP2A)^[35].

While PP2A is defined as the main enzyme of dephosphorylation, the effects of other protein phosphatases have also attracted more and more attention. Calcineurin (PP2B) is a Ca²⁺/calmodulin-dependent protein phosphatase expressed at a high level in brain, and calcineurin deficiency would result in tau hyperphosphorylation^[36]. However, research of Lian QY *et al.* suggested that de-

creased activity of calcineurin, but not the decline of calcineurin protein expression, was the main culprit of tau hyperphosphorylation^[37].

3.2 Activation of the upstream of tau phosphorylation pathway Accumulative evidence has indicated that a number of pathways are involved in the hyperphosphorylation of tau protein. Glycogen synthase kinase-3 β (GSK-3 β) and Cyclin-dependent kinase 5 (CDK5) are proline-directed kinases, which have been demonstrated to be responsible for tau phosphorylation^[38]. GSK-3 β is a predominant kinase that phosphorylates tau mainly at the PHF-1 site epitope (the hyperphosphorylated tau site leading to NFTs)^[38]. Rankin CA *et al.* have found that tau phosphorylation by GSK-3 β may promote tangle-like filament morphology^[39]. CDK-5 can also affect tau phosphorylation. It has been reported that tau is hyperphosphorylated in mice overexpressing CDK-5, leading to spatial memory decline compared with the normal mice^[40].

Mitogen-activated protein kinases (MAPKs) contribute to the formation of microtubules in cells to sustain the normal function. JNK and p38, the 2 members of MAPK family, are involved in tau hyperphosphorylation^[41]. Atzori C *et al.* have found that JNK and p38 are co-localized with hyperphosphorylated tau in the brain^[42], which was further supported by Lagalwar S *et al.*^[43], who found that tau was hyperphosphorylated after the appearance of phosphor-JNK (p-JNK). The research of Ferrer I *et al.* revealed that Ras-induced increase in the phosphorylation of Erk, a member of the MAPK family, was associated with early tau deposition in neurons^[44]. However, Pei JJ *et al.* suggested that aberrant regulation of both phosphatidylinositol-3 kinase (PI3K) and MAPK was involved in tau hyperphosphorylation^[45]. PI3K promotes cell survival and communication by activating Akt kinase. With PI3K activation in neurons, GSK-3 β -dependent hyperphosphorylation of tau could be suppressed^[46]. However, the study of Ryder J *et al.* showed a possible interaction of Akt/GSK-3 β and tau hyperphosphorylation *in vivo*^[47]. Therefore, PI3K inhibits GSK-3 β -induced tau hyperphosphorylation probably through other downstream factors instead of Akt.

On the other hand, Chatterjee S *et al.* have found that

the tau mutants resistant to phosphorylation by MAPK/ PAR-1 are less toxic by increasing affinity to microtubule, compared with the wild type^[48]. Therefore, microtubule binding is an important step in the regulation of tau toxicity. Poppek D *et al.* indicated that tau oxidation might be related to tau phosphorylation, causing the accumulation of tau aggregates^[49].

3.3 Targets screened for anti-tau hyperphosphorylation research The pathways involved in the upstream of protein kinase and in dephosphorylation of tau phospho-

rylation were concluded above. If the balance between tau phosphorylation and dephosphorylation is damaged, tau might be hyperphosphorylated in the brain, leading to the generations of NFTs, and ultimately AD. It is apparent that the ideal targets should be the upstream of the pathways and the factors affecting dephosphorylation. The theoretic targets for anti-tau hyperphosphorylation research are concluded in Table 2. Even though the ideal targets are found, discovering the effective drugs is still an arduous challenge because AD is a multifactorial and heterogeneous disease.

Table 2. The targets for preventing tau hyperphosphorylation

Targets	Drug/Compound	Brief mechanism
Dickkopf-1 (DKK-1)	Undiscovered	To weaken the antagonist on Wnt pathway
P25	Undiscovered	The inhibitor of GSK3 beta
PP2A	Undiscovered	Activating dephosphorylation of PP2A
Prolyl isomerase Pin 1	Undiscovered	Activating Pin 1 to decrease NFTs
GSK-3	Manzamine A	Inhibiting GSK-3 signal pathway
Phosphodiesterases	Undiscovered	To increase the availability of cGMP/cAMP
PTEN (a tumor-suppressor)	Undiscovered	Increasing PTEN expression to decrease NFTs
Akt	Undiscovered	Activating Akt to mediate neurotrophic effects
PI3K	Metallo-complex	Activating PI3K to inhibit GSK-3 beta
AMPK	Undiscovered	Activating AMPK to regulate phosphorylation

PP2A: protein phosphatase 2A. GSK-3: glycogen synthase kinase 3. PI3K: phosphatidylinositol 3-kinase. TLR: Toll-like receptor. AMPK: AMP-activated protein kinase.

4 Conclusion

Until now, controversy still exists concerning whether the aberrant aggregates in the brain may have a toxic or a protective effect^[50]. To date, no conceivable pathway can elucidate clearly the molecular mechanism of NTFs. Thus, AD is always considered as the result of multiple “hits” including alterations in the levels of A β , metals, cholinesterase enzymes, and neuronal gene expression^[51]. However, some new targets in the signal pathways have been discovered and have been shown to ameliorate the symptoms of AD. Based on these targets related with neuronal impairment, some new drugs can be discovered for

AD treatment. As a whole organism, the cells must have complex pathway crosstalks, through which they adapt to the internal or external environment changes. Therefore, if the key original signals that trigger cell dysfunction can be determined, research in AD may be greatly facilitated.

Research on AD is largely concentrated on identifying the molecular mechanisms of AD, but it is also important to identify the consequences of AD. The transgenic model of AD and other methods for AD model establishment have been available, such as the AD model established by *D*-galactose intraperitoneal injection and aluminum trichloride intragastric administration in appropriate doses for 3 months, a patent in our lab. However, it remains elu-

sive whether the model can really represent the pathogenic process of AD. There is still a long way to gain clinical success of AD treatment until the effective drug is discovered or the molecular mechanism is elucidated completely.

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基于 A β 与 tau 蛋白过度磷酸化损伤机制的阿尔茨海默病治疗靶点

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摘要: 阿尔茨海默病(Alzheimer's disease, AD)的发病机制主要包括A β 蛋白表达增高在脑内聚集形成老年斑和tau蛋白过度磷酸化在胞内形成神经原纤维缠结。尽管A β 与tau蛋白的损伤机制一直是AD研究的重点,但目前仍未找到能有效治疗AD 的药物。本文主要概述了A β 蛋白聚集与tau蛋白过度磷酸化对大脑损伤作用的分子机制,并从中寻找治疗AD的潜在靶点,有助于阐明AD发病机理以及寻找有效的AD治疗药物。

关键词: 阿尔茨海默病; A β 聚集; tau蛋白过度磷酸化; 治疗靶点