Regulation of β cleavage of amyloid precursor protein

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Abstract: Alzheimer's disease ranks the first cause for senile dementia. The amyloid cascade is proposed to contribute to the pathogenesis of this disease. In this cascade, amyloid β peptide ($A\beta$) is produced through a sequential cleavage of amyloid precursor protein (APP) by β and γ secretases, while its cleavage by α secretase precludes $A\beta$ production and generates neurotrophic sAPP α . Thus, enhancing α secretase activity or suppressing β and γ cleavage may reduce $A\beta$ formation and ameliorate the pathological process of the disease. Several regulatory mechanisms of APP cleavage have been established. The present review mainly summarizes the signaling pathways pertinent to the regulation of APP β cleavage.

Keywords: Alzheimer's disease; amyloid β peptide; amyloid precursor protein; β secretase

1 Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases among the aged, affecting 26.6 million people worldwide in 2006. It is estimated that by 2050, 1 in 85 persons worldwide would have AD^[1]. Clinically, AD is characterized by memory decline at early time, cognitive impairment during the progression of AD, and brain functional loss at the final stage^[2]. Synaptic dysfunction is thought to be responsible for the clinical symptoms and synapse loss is found to be best correlated with the dementia degree^[3,4]. Histological characterizations of AD include senile plaques composed of $A\beta$ and neurofibrillary tangles composed of hyperphosphorylated tau in brain. Thus, the amyloid cascade hypothesis and tau hypothesis are proposed, suggesting that $A\beta$ or tau is the causative agent of AD^[5]. The amy-

loid hypothesis is supported by the fact that mutation of APP or presenilins, the catalytic component of γ secretase in APP processing, results in more production of $A\beta$ and early onset of familial Alzheimer's disease (FAD)^[6,7]. $A\beta$ is found to be toxic in cultured cells and in animal models^[8,9], and inhibition of $A\beta$ production or enhancement of its clearance can attenuate the AD-like pathology^[10,11].

The cleavage of APP by secretases is shown in Fig. 1. There are 2 types of APP processing, the amyloidosis pathway and the nonamyloidosis pathway^[12]. In the former pathway, APP is first cleaved by β secretase (β -site of APP cleaving enzyme, BACE) into 2 fragments, the secreted amyloid precursor protein β (sAPP β) in the N terminus of APP and β C-terminal fragment (β -CTF, C99 fragment) on the membrane. Then β -CTF is cleaved by γ secretase (mainly composed of presenilin, nicastrin, Aph1 and Pen2), releasing the 39-43aa $A\beta$ peptide and the APP intracellular domain (AICD). $A\beta$ monomer is mainly secreted to extracellular spaces, where it aggregates to oligomers and fibrils^[13], which are the most toxic form of $A\beta$ and the main component of senile plaque, respectively^[8,9]. In the nonamyloidosis pathway, APP

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Fig. 1 Cleavage of APP by secretases. In the amyloidosis pathway, APP is sequentially cleaved by β and γ secretases leading to the production of sAPP β , A β and AICD, while in the non-amyloidosis pathway, APP is sequentially cleaved by α and γ secretases leading to the production of sAPP α , p3 and AICD. sAPP β : the secreted amyloid precursor protein β . AICD: APP intracellular domain. β -CTF: β C-terminal fragment.

is first cleaved by α secretase (ADAM10, 17 and 9) at 16aa of A β sequence, shedding secreted amyloid precursor protein α (sAPP α) and leaving α C-terminal fragment (α -CTF, C83 fragment). Then α -CTF is cleaved by γ secretase into p3 and AICD. Since APP cleavage by α secretase prevents A β generation and sAPP α is found to be neurotrophic, the nonamyloidosis pathway seems to be protective.

APP cleavage by different secretases has been found to be differentially subcellularly localized^[14]. After leaving endoplasmic reticulum (ER) and maturation in Golgi, a portion of APP is cleaved in trans-Golgi network (TGN), where β secretase competes with α secretase. The unprocessed APP is transported to cell membrane, where α secretase carries out cleavage. The still uncleaved APP is internalized to endosome, where it is processed by β and γ secretases (Fig. 2). Extra- or intracellular signals regulating the sorting of APP and secretases to different subcellular localizations are closely correlated with A β production, providing opportunities for experimental and clinical interventions of A β formation. The present review mainly summarizes the signaling pathways that regulate β cleavage of APP, a rate-limiting step in A β generation.

2 Regulation of APP processing

2.1 APP APP belongs to the type I membrane protein family, which also includes the amyloid precursor-like proteins (APLPs), APLP1 and APLP2. All these members have a large extracellular domain, a transmembrane domain and a short cytoplasmic domain^[14]. Alternative splicing of APP mRNA gives rise to 6 isoforms of APP, ranging 365-770aa in different tissues. APP695, APP751 and APP770 are 3 major isoforms expressed in brain, with APP695 being mainly in neurons^[15]. The function of APP is attributed to its cleavage segments, sAPP α and AICD^[14]. sAPP α may promote neurite outgrowth, synaptogenesis, and learning and memory, while AICD could regulate the expression of some genes, including p53 and neprilysin. APP undergoes complex post-translational modifications such as N- and O-glycosylation, phosphorylation, and tyrosine sulfation^[14]. Cytoplasmic phosphorylation, protein interaction and extracellular signals may alter the subcellular localization of APP, and modify APP β cleavage and A β production.

2.2 Phosphorylation of cytoplasmic domains There are 8 potential phosphorylation sites in the APP cytoplasmic

Fig. 2 Subcellular localization of $A\beta$ production. **A:** After leaving endoplasmic reticulum, APP is sorted to Golgi, where β secretase competes with α secretase to cleave a portion of APP into $sAPP\beta$ and C99. C99 is then cleaved by γ secretase to produce $A\beta$ that is released into the extracellular space. **B:** The unprocessed APP is transported to plasma membrane, where α cleavage preferentially occurs and $sAPP\alpha$ is released. **C:** The still-uncleaved APP is internalized through endocytosis to endosome, where it is processed by β and γ secretases. **D:** Endosome is the main localization of β cleavage and $A\beta$ production. The released $A\beta$ is secreted to extracellular spaces.

domain^[16]. Some of the potential sites are within the 682YENPTY687 motif, a canonical endocytic signal for membrane-associated receptors. Mutation of Tyr682, Asn684, or Pro685 has been shown to inhibit the internalization of APP and decrease $A\beta$ generation. Some other potential phosphorylation sites are within the 653YTSI656 motif, which is also an endocytic/basolateral sorting signal. Phosphorylated Thr654 and Ser655 have been found in several cell lines and in adult rat brain^[17]. CaMKII, protein kinase C (PKC), APP kinase I and abl are involved in the phosphorylation of these 2 motifs^[18].

Another potential site is Thr668, which could be phosphorylated by a number of protein kinases, including GSK3 β , JNK3, Cdc2 and Cdk5. These phosphorylations have been shown to alter $A\beta$ production, indicating that stress and cell cycle could affect APP phosphorylation and processing^[18].

Furthermore, phosphorylated APP (P-APP) at Thr668 is significantly increased in human AD brain^[16]. A recent immunohistochemical study reveals that P-APP co-localizes with BACE1 in enlarged endosomes of AD hippocampal neurons and primary cultured cortical neurons. Additionally, β -CTFs are preferentially phosphorylated at Thr668 over α -CTFs, and $A\beta$ generation is significantly reduced by mutation of Thr668 to Ala or by treatment with Thr668 kinase inhibitors. However, a recent study^[19] using the Thr668Ala knock-in mice has revealed that there are no significant differences in subcellular localizations or levels of full length APP, α -CTF, β -CTF, $sAPP\alpha$, $sAPP\beta$, $A\beta$ 40 or $A\beta$ 42 between the Thr668Ala knock-in mice and the control mice. The discrepancy might be explained by the fact that unlike the APP overexpression system used in previous reports, the Thr668Ala knock-in mice express APP at the endogenous level. Thus, phospho-

rylation of Thr668 may not affect A β level in physiological mouse brain, but could modify A β production if APP level is high.

2.3 Protein interaction The YENPTY motif mentioned above is also important for the binding of APP to a class of cytoplasmic proteins containing a phosphotyrosine binding (PTB) domain, such as Fe65, X11s, JIP, mDab, and Numb, and some of these interactions play a role in A β generation^[20]. Fe65 is an adaptor protein enriched in brain, and the interaction of PTB domain with APP YENPTY motif may be dependent on Thr668 phosphorylation, as phosphorylated Thr668 causes a dramatic conformational change and prevents the binding of Fe65^[21]. APP and Fe65 co-localize in the perinuclear region, and overexpression of Fe65 translocates APP to the plasma membrane, thus blocking the β cleavage and reducing A β formation^[22]. Crossing APP mice with Fe65 mice reduces A β level in the double transgenic offspring, indicating that Fe65 could modulate APP cleavage *in vivo*^[23]. Moreover, the effect of Fe65 may require the presence of low density lipoprotein receptor-related protein (LRP), since the LRP-Fe65-APP trimeric complex is detected and Fe65 is able to enhance sAPP α secretion only in the presence of LRP^[24].

The X11 proteins (X11s) are a family of adaptor proteins firstly termed munc-18 interacting proteins (Mints) for their binding to a neuronal synaptic protein Munc18. However, X11s also bind to some other proteins, most notably APP, neuexins and EGFR^[25]. Unlike Fe65, the binding of X11 to APP seems not to depend on Thr668 phosphorylation^[20]. Overexpression of X11 α or X11 β prolongs the half-life of APP and inhibits the formation of A β as well as sAPP α ^[26]. The *in vivo* effects have been examined and overexpression of either X11 α or X11 β in Tg2576 mice reduces A β level and amyloid plaques^[27,28]. Although the underlying mechanism is not clear, the findings that both A β and sAPP α levels are decreased suggest that the binding of X11s may prevent the access of APP to both α and β secretases.

The Disabled (*Dab*) gene family encodes adaptor proteins which are important for embryogenesis and for the correct positioning of neurons within laminar structures throughout the brain^[29]. The interaction of APP with mDab1 increases the cellular level of mature APP, thus promoting its processing

by the secretases and the elevation of A β level. Since Fe65, X11s and mDAB all bind to the YENPTY motif of APP, they may compete for the binding with APP and the competition may be related to APP cleavage in various conditions^[30,31].

Neuronal sorting protein-related receptor SorLA also interacts with APP and decreases A β formation^[32]. SorLA is an adaptor protein for retromer, which transports type I membrane protein from endosome to TGN^[33]. The interaction of SorLA with the retromer mediates the recycling of APP from endosome to TGN, precluding the preferential β cleavage in endosome. Downregulation of SorLA enhances A β formation in cultured cells and in mouse AD models^[34,35]. The level of SorLA is reduced in sporadic AD patients, indicating that SorLA may play important roles in A β production and AD pathogenesis. In addition, singlenucleotide polymorphisms (SNPs) in SorLA are associated with late onset AD and these SNPs are found to govern cell type- or tissue type-specific expression level of SorLA, further indicating the importance of SorLA in AD pathogenesis^[36]. Recently, brain-derived neurotrophic factor (BDNF) has also been found to be the major inducer of SorLA gene transcription through the ERK pathway, and SorLA expression is significantly downregulated in BDNF knockout mice^[37]. Therefore, the decrease in BDNF level in AD brain may explain the reduction of SorLA level in AD patients.

2.4 Neuronal activity A β level has been found to be related with neuronal activity, and enhanced synaptic transmission may increase A β formation. For example, brain regions with the highest basal activity, such as parts of the frontal and parietal lobes and posterior cingulate cortex, exhibit the highest level of amyloid plaques^[38]. Besides, patients with temporal lobe epilepsy develop senile plaques in the temporal lobe in their thirties, much earlier than do the control patients^[39]. Additionally, environmental enrichment, a model used to enhance cognitive and social stimulations and thus neuronal activity, exacerbates amyloid plaque formation in APP/PS1 transgenic mouse^[40]. In cultured organotypic slices from APP transgenic mice, decreasing neuronal activity reduces A β level, whereas increasing activity elevates A β level^[41]. The underlying mechanism seems to involve clathrin-mediated endocytosis. APP has been reported to be within the vesicles

containing synaptic proteins, suggesting that endocytosis of APP shares a common pathway with that of synaptic proteins. Indeed, a dynamin dominant negative inhibitory peptide (dynamin-DN) inhibits endocytosis of clathrin-coated vesicles and A β secretion induced by synaptic transmission^[42]. Thus, neuronal activity may enhance clathrin-mediated endocytosis, delivering more APP from plasma membrane to endosome, where APP is cleaved by β and γ secretases into A β peptide.

2.5 Metal ions The metal hypothesis of AD is based on the observation that the plaques are rich in metal ions that can interact with A β ^[43]. Studies show that zinc and copper could promote the aggregation of A β from monomers to oligomers and large fibrils, and drugs targeting metal ions could attenuate the AD symptoms in AD mice models and patients^[19,44,45]. Recently, the effects of magnesium on APP processing and A β generation have been investigated, and the results show that high concentration of extracellular magnesium reduces β -CTF and A β secretion, while low level of magnesium elevates β -CTF and A β secretion. The underlying mechanism seems to involve the modulation of APP trafficking, as magnesium dose-dependently increases APP level on plasma membrane, which favors α thus precluding β cleavage^[46].

3 Regulation affecting β secretase

3.1 BACE1 The molecule that functions as β secretase has been cloned independently by 5 laboratories^[47-51]. BACE1, also called memapsin 2 or Asp2, is a 501aa type I membrane aspartic protease of the pepsin family. BACE2 is a close homolog of BACE1. BACE1 functions as β secretase, and knockout of BACE1 in mice totally abolishes β -CTF and A β productions^[52]. Unlike BACE1, BACE2 may carry out α cleavage instead^[53]. BACE1 knockout does not appear to dramatically affect embryonic development or gross behavior of adult mice^[54,55], which indicates that inhibition of BACE1 activity may be tolerated and could be a viable method for suppression of A β generation and AD treatment. Unlike APP and presenilins which have FAD-linked mutations, no genetic variant of BACE1 has been found. However, several groups have reported that the level or activity of BACE1 is elevated in AD brain, indicating that upregulation of β cleavage may

lead to the pathogenesis of sporadic AD^[56,57].

3.2 Transcriptional and translational regulation BACE1 is documented as a stress-induced protease and its expression is elevated under hypoxia, ischemia, inflammation and trauma conditions. The promoter of BACE1 gene contains binding sites for a variety of transcriptional factors, including NF κ B, cAMP response element-binding (CREB), hypoxia-inducible factor 1 (HIF1), heat shock factor 1 (HSF1), STAT1, Sp1, activator protein 1 (AP1), activator protein 2 (AP2), nuclear factor of activated T cells (NFAT), PPAR γ , estrogen and glucocorticoid receptors^[58]. Mechanistic studies have linked stress responses with specific transcriptional factors in BACE1 regulation. Hypoxia represents a shortage of oxygen in the body and brain is especially susceptible to hypoxia. HIF1 is a hypoxia-induced transcriptional factor regulating expression of genes involved in oxygen homeostasis through hypoxia-responsive element (HRE) in the promoters. A functional HRE is present in BACE1 promoter and its binding with HIF1 mediates the hypoxia-induced elevation of mRNA and protein levels of BACE1 and A β generation^[59]. Oxidative stress results from accumulation of reactive oxygen species which has been proposed to contribute to aging and AD development. Oxidative stress induced by 4-hydroxynonenal (HNE) and H₂O₂ in cell models or by cerebral ischemia/reperfusion in mice can increase BACE1 transcription, and JNK/AP1 activation is essential for this upregulation^[60]. Furthermore, elevated JNK phosphorylation has been detected in human AD brain^[61], indicating the importance of JNK/Jp1 for A β overproduction. On the other hand, A β itself may stimulate the transcription of BACE1 and induce a positive feedback to enhance the β cleavage of APP and A β formation. A β could disrupt the intracellular calcium homeostasis and activate NFAT through calcineurin to translocate into nucleus and increase the BACE1 transcription. Elevated BACE1 level has been detected around amyloid plaques in AD mice^[62]. A β may also induce BACE1 promoter transactivation by NF κ B^[63].

The translational regulation of BACE1 expression under energy deprivation has also been studied^[64]. The protein level of BACE1 in HEK293 cells cultured without glucose is increased, while the mRNA level and the half life of BACE1

remain unchanged, indicating that the elevated BACE1 protein level might result from enhanced translation. Indeed, eukaryotic translation initiation factor 2 (eIF2) phosphorylation is enhanced under glucose deprivation, while inhibition of eIF2 phosphorylation blocks the BACE1 increase. In a chronic energy deprivation model of TG2576 mice, eIF2 phosphorylation, BACE1 and A β levels, and the number of plaques are all increased^[65]. Phosphorylation of eIF2 is also enhanced in human AD brain and positively correlates with BACE1 level and plaque load, indicating that impaired brain energy metabolism and translational regulation of BACE1 may play important roles in AD development.

3.3 Protein interaction Several proteins interacting with BACE1 have been identified, including prostate apoptosis response 4 (Par-4), reticulon (RTN) 3/4, heparan sulfate, Golgi-localized, gamma-ear-containing, ADP ribosylation factor-binding proteins (GGA), sorting nexin 6 (SNX6) and δ -opioid receptor (DOR)^[58]. All these interactions can modulate A β production. Par-4 is a leucine zipper protein initially found to be a mediator of neuronal degeneration in AD^[66]. Par-4 expression is dramatically increased in hippocampal and cortical neurons in AD brain, and could be induced in cultured neurons treated with A β . Overexpression of Par-4 significantly increases A β 42/A β total ratio after trophic factor withdrawal, and this effect is blocked by co-expression of the leucine zipper domain, indicating that the modulation activity of Par-4 may depend on its interaction with other proteins^[67]. Recently, the direct binding of BACE1 cytoplasmic domain with Par-4 C-terminus has been identified, and downregulation of Par-4 by siRNA could decrease the levels of β -CTF and A β . Yet, how the interaction between Par-4 and BACE1 modulates β cleavage is unclear.

RTNs are a group of conservative proteins residing mainly in ER and functioning in ER-Golgi trafficking, vesicle formation and membrane morphogenesis. RTN4, also known as Nogo, inhibits neurite outgrowth after injury. The interactions between BACE1 and RTN3/4 are identified using co-immunoprecipitation and proteomics analysis, and these bindings may depend on the C-terminus of BACE1, since truncation of the N terminal catalytic domain does not disrupt the interactions^[68,69]. Overexpression of RTN3 inhibits BACE1

activity, β -CTF and sAPP β levels, and dose dependently decreases A β production, while downregulation of RTN3 expression elevates β -CTF and A β levels. RTN4 has a similar effect on A β generation. The interaction of BACE1 with RTNs might block its access to APP and thus APP cleavage, since a previous study found that less APP was co-immunoprecipitated with BACE1 when more RTN3 interacted with BACE1^[68].

Heparan sulfate interacts and co-localizes with BACE1 in the Golgi and at the cell surface^[70]. sAPP β and A β levels are downregulated by overexpression of heparan sulfate, or increased when endogenous heparan sulfate synthesis is inhibited. Interestingly, the inhibitory activity is dependent on saccharide size and specific structural characteristics. The underlying mechanism also involves blocking access of substrate to the active site of BACE1.

GGAs are a family of adaptors implicated in the intracellular protein sorting. GGA3 is necessary for the delivery of EGFR from endosome to lysosome for degradation. BACE1 is mainly localized in TGN and endosome, and subject to degradation in lysosome or by a proteasome-dependent pathway. The trafficking of BACE1 from endosome to lysosome depends on GGA^[71]. BACE1 has a DISLL motif (residues 496-500) in its cytoplasmic domain, and this acidic di-leucine sequence mediates its binding to the VHS domain of GGA. Mutation of the DISLL motif interrupts the interaction between BACE1 and GGA, and potentiates the accumulation of BACE1 in endosome, increasing the total level of BACE1. On the other hand, silencing of GGA3 by RNA interference (RNAi) also enhances the levels of BACE1, β -CTF and A β . Thus, GGA may be implicated in the trafficking of BACE1 from endosome to lysosome for its degradation. Interestingly, GGA3 is shown to be cleaved by caspase 3 during apoptosis and GGA3 level is decreased in the brain of AD patients^[72]. This may partially explain how BACE1 level is elevated in AD brain and indicates that protection of neurons against apoptosis could attenuate APP cleavage by BACE1 and A β production.

SNX6 is a newly identified BACE1-associated protein and a putative component of retromer. Knocking down of SNX6 with RNAi elevates the levels of sAPP β and β -CTF,

resulting in increased A β production. Furthermore, SNX6 reduction leads to elevated steady-state BACE1 level and increased retrograde transport of BACE1 from endosome to TGN, suggesting that SNX6 modulates the basal level and retrograde trafficking of BACE1, thereby regulating β cleavage of APP and A β formation^[73].

DOR is a G-protein coupled receptor (GPCR) and its activation can enhance γ -secretase activity and accelerate A β production. Recently, DOR has been reported to form a complex with BACE1 and γ -secretase. Activation of DOR facilitates endocytosis of this complex, and therefore enhances the activities of BACE1 and γ -secretase, resulting in A β generation. Chronic treatment of AD mice with DOR antagonist or knocking down of DOR can reduce the activities of BACE1 and γ -secretase, alleviate A β pathology and improve deficits in spatial learning and memory^[74].

3.4 Lipid rafts and cholesterol Lipid rafts are specialized membrane microdomains composed of glycosphingolipids and protein receptors, and function as organizing centers for the assembly of signaling molecules for specific cellular processes. Cholesterol interacts preferentially with sphingolipids and assists the formation of lipid rafts. Lipid rafts generally contain twice the amount of cholesterol found in the surrounding membrane bilayer. Both APP and BACE1 have been found to be within lipid rafts, and β cleavage preferentially occurs in lipid rafts where they are close to each other^[75]. Depletion of cholesterol disrupts the compartmentalization of APP and BACE1 to lipid rafts, thus inhibiting A β formation, while elevation of cholesterol enhances A β production. Animals fed with cholesterol show enhanced A β level, while the cholesterol-lowering drug simvastatin strongly reduces A β formation *in vivo*^[76,77]. Epidemiological studies also show that patients with long-term statin treatment have a lower prevalence of AD, suggesting that inhibition of cholesterol may reduce A β production and the risk of AD.

4 Conclusion

Since the first report showing the toxicity of A β in cultured cells^[78], the adverse effect of A β has been widely demonstrated both *in vitro* and *in vivo*, and A β has been indicated as a final agent of AD pathogenesis^[8,9]. A β is physi-

ologically derived from β and γ cleavage of APP and degraded by a number of enzymes^[79], although the normal function of A β remains still not well understood. A β accumulates when the balance between its production and clearance is broken, and FAD-linked mutations of APP and presenilins could enhance A β production and lead to early onset AD, suggesting that A β overproduction is able to induce the disease onset. As β cleavage of APP is the rate-limiting step in A β generation, much focus has been put on the regulation of APP β cleavage.

APP is the substrate of BACE1 that mediates β cleavage. Lipid rafts and protein interactions could affect the accessibility of APP to BACE1 and thus the β cleavage. The optimum pH for BACE1 activity is approximately 4.5 and endosome has such an acidic environment. Thus, the signaling pathways enhancing subcellular localization of APP and BACE1 to the endosome would enhance APP β cleavage and A β formation, and those pathways trapping APP on the cell membrane or recycling it back to TGN could inhibit β cleavage. Transcriptional and translational regulation of BACE1 expression, or signals that regulate its degradation, can influence the cellular level of the enzyme and APP β cleavage.

Many clinical trials based on 'amyloid cascade hypothesis' have been conducted, using either secretase inhibitors/modulators to decrease A β production or A β immunization to clear amyloid plaques^[80,81]. However, to date, all the trials have failed, and the negative results might be due to the late intervention of the disease (the recruited patients are in advanced stage of dementia). This emphasizes the importance of early diagnosis of the disease and of searching adequate biomarkers before disease progression. The clinical failure also suggests that more studies on the regulation of APP cleavage and A β production are needed, and new drug targets other than secretases should be investigated.

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淀粉样前体蛋白 β 切割的调控

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摘要: 阿尔茨海默病是造成老年人痴呆的首要因素。淀粉样蛋白级联假说认为 β 淀粉样蛋白是阿尔茨海默病的致病因子, 其在大脑中的含量高低对疾病的发生有重要意义。 β 淀粉样蛋白由淀粉样前体蛋白相继经 β 和 γ 分泌酶切割产生, 而 α 分泌酶的切割既排除了 β 淀粉样蛋白的形成, 又能产生具有神经保护作用的片段。因此, 抑制 β 或 γ 切割, 或者增强 α 切割, 都可以减少 β 淀粉样蛋白的积累, 改善阿尔茨海默病的病理表现。淀粉样前体蛋白切割的调控机理, 目前已被广泛研究。本文就淀粉样前体蛋白 β 切割的调控机理作一综述。

关键词: 阿尔茨海默病; β 淀粉样蛋白; β 淀粉样前体蛋白; β 分泌酶