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REVIEW ARTICLE

Post-Translational Modifications of BACE1 in Alzheimer's Disease

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Abstract: Beta-Amyloid Cleaving Enzyme1 (BACE1) is a monospecific enzyme for the key rate-limiting step in the synthesis of beta-amyloid(Aβ) from cleavage of amyloid precursor protein (APP), to form senile plaques and causes cognitive dysfunction in Alzheimer's disease (AD). Post-translation modifications of BACE1, such as acetylation, glycosylation, palmitoylation, phosphorylation, play a crucial role in the trafficking and maturation process of BACE1. The study of BACE1 is of great importance not only for understanding the formation of toxic Aβ but also for the development of an effective therapeutic target for the treatment of AD. This paper review recent advances in the studies about BACE1, with focuses being paid to the relationship of Aβ, BACE1 with post-translational regulation of BACE1. In addition, we specially reviewed studies about the compounds that can be used to affect post-translational regulation of BACE1 or regulate BACE1 in the literature, which can be used for subsequent research on whether BACE1 is a post-translationally modified drug.

Keywords: Alzheimer`s disease, APP, Aβ, BACE1, neurodegenerative diseases, post-translational modification.

1. INTRODUCTION

Alzheimer's disease (AD) is an age-depended neurodegenerative disease with progressive cognitive deficits [1, 2], with senile plaques, neurofibrillary tangles and synaptic loss being characteristic neuropathological hallmarks [3]. We are facing the paradoxical fact that the morbidity of AD increases rapid and the effective therapeutic drugs remain inadequate. Regrettably, the pathogenesis is still unclear [4]. Mounting evidences suggest that extracellular deposition of beta amyloid (Aβ) plays a leading role in the pathological manifestations of AD [5-7]. The β-secretase 1 (BACE1) is a necessary enzyme for the rate-limiting step when amyloid precursor protein (APP) is cut into Aβ. Unfortunately, the approaches and drugs which directly inhibit BACE1 have failed in clinical studies because of side effects or inadequate clinical benefit [8, 9]. Recent research has shown that neurotoxicity of Aβ is mediated by soluble oligomeric forms rather than insoluble aggregates [10, 11]. It is known that post-translational modifications of BACE1, including glycosylation, phosphorylation, palmitoylation and so on, are required to get the enzymatic function of cleaving APP [12], which is an important process for the formation of soluble oligomeric or insoluble aggregates of Aβ. This means drugs that inhibit Aβ production by regulating the post-translational modifications of BACE1 is promising and feasible. Here we will review recent advances on the role of Aβ in AD pathogenesis, the relationship between BACE1 and AβO, and the effects of post-translational modifications of BACE1 in Aβ production.

2. Aβ AND AD PATHOGENESIS

2.1. Origin and Function of Aβ

Aβ, a kind of 39-43 amino acids peptide, was firstly considered one of antimicrobial peptides (AMPs) which are related to defensive strategy of lower organisms and human immunity of humans [13]. AMPs are widely expressed and abundantly distributed in the brain, and in other immune-privileged tissues where actions of the adaptive immune system are constrained. Synthetic Aβ peptides have been found to exert antibacterial activity against Gram-negative and Gram-positive bacteria and the yeast Candida albicans *in vitro*. And Aβ peptides have also been demonstrated to protect against meningitis in genetically modified mice and to increase survival of transgenic *C. elegans* infected with Candida *in vivo* [14], and this activity of Aβ is isoform-specific, with Aβ42 showing greater potency than that of Aβ40 [15]. In addition, AMP dysregulation has been shown to result in host cytotoxicity, chronic inflammation and neurodegenerative disease such as AD [16, 17].

It is well known that Aβ aggregates are the main constituent of senile plaques in the brains of AD patients. Aβ

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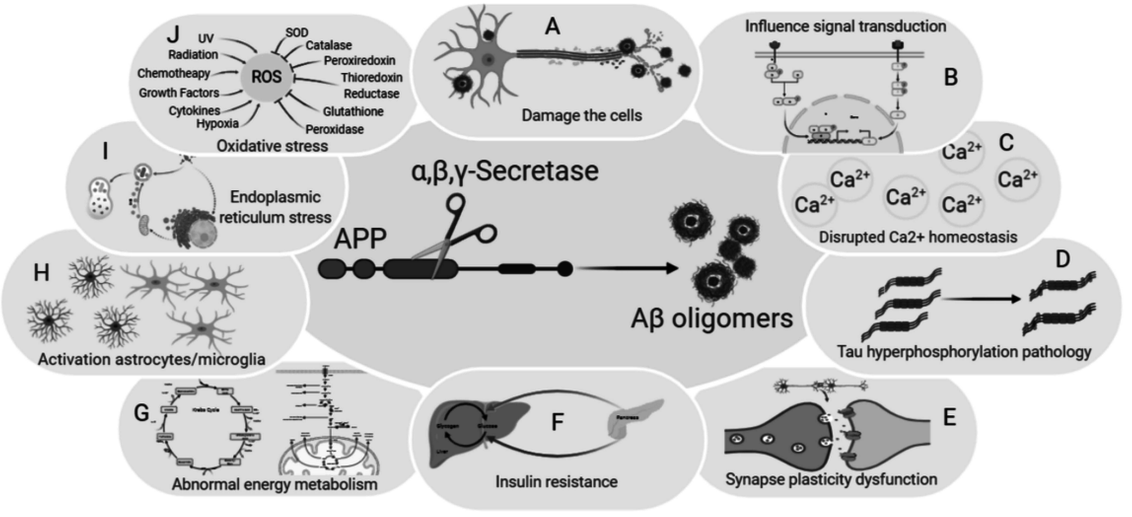

Fig. (1). Amyloid beta oligomers in Alzheimer's disease pathogenesis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

can be divided into soluble amyloid-β oligomers (AβO) and fibrosis Aβ amyloid on the basis of the aggregation state, however, only the oligomerization of fibrosis Aβ is regarded as neurotoxins and involved in synaptic dysfunction and cognitive impairment in AD [18]. The soluble AβO was long ignored until fairly recently, when studies found that amyloid burdens were not correlated well with the premortem cognitive decline on AD patients, instead, the median levels of AβO in cerebrospinal fluid from AD patients are 30-fold higher than those from non-demented individuals [6]. Another line of evidence is that a single injection of a humanized AβO-specific antibody (30μg) could suffice to rescue memory performance in 5xFAD TG mice [11]. At present, it is now widely accepted that soluble AβO, instead of the fibrosis amyloid burdens, is synaptotoxious that accumulate in AD brains [19].

2.2. Toxicity of AβO

Increasing evidences have suggested that soluble AβO is the major neurotoxicity in AD [20, 21]. There are two kinds of hypotheses about the mechanism of neurotoxicity. One is called the bilayer insertion hypothesis, which assumes that soluble AβO can form annular structures which can be inserted into the cell membrane and induce unregulated efflux/influx through the created pores and finally damage the cells (Fig. **1-A**). But this hypothesis cannot explain the specificity of AβO attachment, which is a major challenge to this hypothesis. The other well accepted hypothesis is aberrant cellular signaling, which suggests that soluble AβO can bind to the membrane and induce its endocytosis and deposit within organelles, then damage nerve cells, influence signal transduction, disrupted Ca^{2+} homeostasis, provoke CNS insulin resistance, *etc.* [22]

It is found that accumulation of exogenous soluble AβO at synapses can cause abnormal transmembrane signal selectivity in neurons (Fig. **1-B**). There are three main reasons, one is that the membrane proteins are disrupted by high affinity multi-component toxin complex, which are formed by AβO attaching to a set of high-affinity binding proteins and then recruiting some low-affinity toxin receptors (PRPS, mGLuR5 and RANG. *etc*) [23]. Another one is that AβO can directly or indirectly over-activate postsynaptic NMDARs by impairing glutamate up-take from the extra-synaptic spaces, which binds to the PrPC-mGLU5 receptor complex to phosphorylate and trigger downstream Fyn [24], or results in Ca^{2+} influx, disrupt the Ca^{2+} homeostasis (Fig. **1-C**). The activation of the Fyn can activate the eEF2 (impair LTP) and Pyk2 (regulate synaptic plasticity) simultaneously to impair synaptic deficit [25, 26]. The third way is that AβO can disturb the expression and activity of Akt, ERK, JNK, P38 and some other downstream protein kinases. In addition, AβO can induce Tau hyperphosphorylation and Tau oligomerization both *in vitro* and *in vivo*, which leads to synaptic damage and reduction in the number of synapses [27-29] (Fig. **1D, E**). With all these pathways, AβO can inhibit synaptic plasticity through abnormal cellular signal transduction, and ultimately lead to nerve cell-specific death [21, 30-32].

CNS insulin signaling might also play a role in AβO formation and AβO neurotoxicity. AβO in turn, can impair CNS insulin signaling by competitively inhibiting the binding of insulin-to-insulin receptors and directly leads to insulin resistance (Fig. **1-F**), which form a vicious circle to build up AβO in intracellular and extracellular of CNS [33-34]. When AβO down-regulates insulin signaling, GSK3β activity is elevated, which can increase the level of p-Tau. Besides, AβO can not only lead to a slow, time-dependent decrease in ATPase activity to cause energy metabolism disorders (Fig. **1-G**) [35], but also induce the activation and neuroinflammation of astrocytes and microglia in CNS (Fig. **1-H**) [36]. In addition, AβO can damage the

neurons by an upregulation in both oxidative stress and ER stress (Fig. **1I, J**). In all, these events of cellular damage caused by soluble AβO can initiate the death of nerve cells, and AβO is considered as the proximal toxins responsible for synaptic dysfunction and neuron damage, as well as cell death in AD [37-39].

3. BACE1 and AβO

The treatment strategies for AD patients via Aβ clearance have been recently questioned and challenged due to its poor clinical effects, together with the difficulty to reliably measure AβO in body fluids and tissues [4, 22]. Considering that the key role of soluble AβO in AD pathology, prevention the formation of Aβ becomes even more important than prevention its accumulation and aggregation [9, 40, 41]. BACE1, the key rate-limiting enzyme in the formation of both soluble AβO and fibrosis Aβ, plays crucial role in Aβ generation.

BACE1, beta-site amyloid precursor protein [APP] cleaving enzyme I, is a type I transmembrane aspartyl protease which was identified and named in 1999 [42]. BACE1 is widely expressed in the CNS, particularly in neurons, oligodendrocytes, astrocytes, which are the major sites of Aβ generation [43, 44]. This enzyme is predominantly localized in acidic intracellular compartments (such as late Golgi/TGN and endosomes), and the optimum enzymatic activity is around pH 4.5 [43]. BACE1 is first synthesized as a 501 amino acid immature precursor protein (proBACE1) in endoplasmic reticulum (ER) and matured in Golgi apparatus where its pro-domain (residues 1-21) is removed by furin-like proprotein convertases [43]. BACE1 fulfills most of the requirements for a candidate β-secretase, and induces Aβ production by the successive cleavage of β- and γ-secretase of APP [45].

Amyloid precursor protein (APP) is a single-pass transmembrane protein with large extracellular domains, and can be generally cleaved through non-amyloidogenic and amyloidogenic pathways (Fig. **2**). The non-amyloidogenic pathway is mainly cleaved by α-secretase and γ-secretase; while the amyloidogenic pathway is cleaved by β-secretase and γ-secretase. Through non-amyloidogenic pathway, APP is cut into soluble APPα (APPsα) and a peptide with 83 amino acids in length (CTF83) by α-secretase. Afterwards, CTF83 is cleaved by γ-secretase to release a small p3 fragment into the extracellular space and the APP carboxy-terminal fragment59 (C59) into the cytoplasm. Through amyloidogenic pathway, APP was first cleaved by β-secretase (BACE1) to release soluble APPβ (APPsβ) and a peptide with 99 amino acids in length (CTF99). BACE1 initiates Aβ generation by cleaving APP within the extracellular domain of APP between Met596 and Asp597 sites, to generate the N-terminus-fragment of Aβ, shed a large part of the ectodomain of APP (APPsβ) and generate an APP carboxy-terminal fragment (βCTF or C99), which acts as the immediate substrate for γ secretase [46]. Then, β-CTF is cleaved into C-terminal heterogeneous Aβ peptides (ranging from 38 to 43 residues

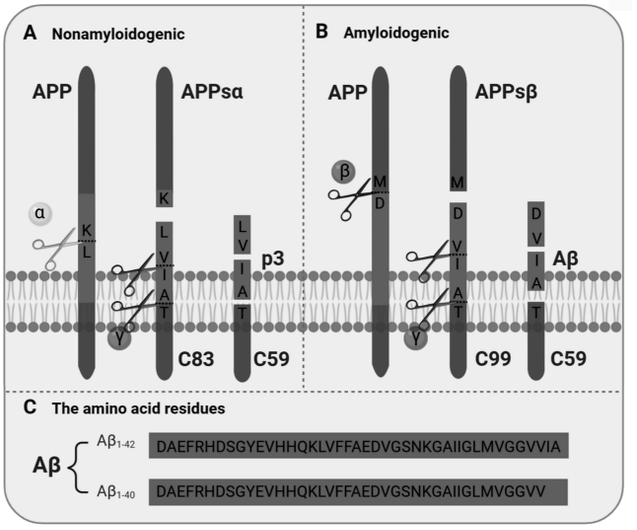

Fig. (2). Processing of APP by the secretases. **A**) In the nonamyloidogenic pathway, APP is first cleaved by α-secretase within the Aβ sequence, which releases the APPsα ectodomain. Further processing of the resulting carboxyl terminal by γ-secretase results in the release of the p3 fragment. **B**) The amyloidogenic pathway is initiated when β-secretase cleaves APP at the amino terminus of the Aβ peptide and releases the APPsβ ectodomain. Further processing of the resulting carboxy-terminal fragment by γ-secretase results in the release of Aβ. **C**) The amino acid residues from various cleavage of APP. Aβ and p3 fragments of differing lengths are produced by processing of APP at two different sites by γ-secretase. Abbreviations: Aβ, amyloid-β; APP, amyloid precursor protein; APPsα, soluble amyloid precursor protein-α; APPsβ, soluble amyloid precursor protein-β; C83, carboxy-terminal fragment 83; C59, carboxy-terminal fragment 59; C99, carboxy-terminal fragment 99. The APP progressing was referred to literature [51] and created on BioRender.com. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

in length) and cytosolic APP intracellular domains by γ-secretase at multiple sites [47], which occurs within the hydrophobic environment of biological membranes [48]. Aβ is liberated into extracellular fluids such as cerebrospinal fluid (CSF) [48, 49]. Both APPsα and APPsβ have benefit properties, such as increasing neurite outgrowth *in vitro*, protecting neuron and stimulating proliferation of adult neural progenitors [50].

In addition to acting as an enzyme in a key rate-limiting processing step of Aβ generation, BACE1 also regulates axon myelination in the peripheral nervous system through participating the proteolytic processing of Neuregulin-1 [52-53]. Although some studies have shown that moderate inhibition of BACE1 activity may be beneficial to AD treatment, BACE1 inhibition is beneficial or not for AD patients is controversial up to now. Evidences supporting the beneficial roles came from animal experiments and clinical studies, for instance, BACE1 heterozygous knockout mice have no reported abnormal phenotypes, and reduced Aβ deposition. One study reported that BACE1 knockout mice showed a 12% decrease in Aβ level in young 5XFAD APP/PS1 mice, and did not show any major behavioral, morphological, or developmental deficit [54, 55]. Another study reported that knockout of BACE1 completely blocked the generation of Aβ and had a minor impact on mouse growth or overall functions since $BACE1^{+/-}$ mice appear normal [56, 57]. Similar studies in humans reported a rare mutation at the BACE1 cleavage site of APP [A673T] resulted in an approximately 40% reduction in the formation of Aβ production in Icelanders; and these people showed a significant reduction for Aβ aggregates, and five- to seven-fold reduced risk of developing AD, and greater resilience to cognitive dysfunction in elderly individuals [58, 59]. However, owing to that BACE1 deficiency can induce hypomyelination of peripheral nerves and aberrant axon segregation of small-diameter axons by Schwann cell processes within Remake bundles [52, 53], there is growing concern that complete inhibition of BACE1 may have serious adverse effects. Clinical trials targeting at inhibiting BACE1 in AD patients found that these inhibitors have the potent in reducing Aβ in human CSF or plasma by as much as 90% during trials, however the trials have failed to proceed because of BACE1 selectivity issue or intolerable toxicity [60-64].

4. POST-TRANSLATIONAL MODIFICATIONS OF BACE1 AND Aβ PRODUCTION

After a series of post-translational modifications in ER and Golgi apparatus, BACE1 is matured to have the function of cleaving APP [65]. During BACE1 maturation, four sites were N-glycosylated and seven Lys residues were acetylated in ER [66], meanwhile, four C-terminal Cys residues for lipid raft localization were deacetylated and palmitoylated in Golgi apparatus [67]. Besides, Lys residues are also the targets for ubiquitination, so BACE1 activity is post-translationally regulated via ubiquitination, because mutation of this residue impairs its endocytosis to lysosomes for degradation, reduces the proteasomal degradation of BACE1, and affects APP processing at the β site, as well as Aβ production [68, 69]. Ser498 phosphorylation facilitates reposition of BACE1 from endosome to Golgi apparatus. and Thr252 phosphorylation increases the activity of BACE1. SUMOylation inhibits the degradation of BACE1 in the lysosome. These post-translational modifications of BACE1 affect the production of Aβ by affecting enzyme activity, substructure localization, and hydrolysis. Current knowledge on these regulatory pathways and their implications on Aβ production or AD therapy are discussed below in detail (Figs. **3** and **4**).

4.1. Acetylation

Acetylation is one kind of BACE1 post-translational modification that occurs in ER. After pro-BACE1 is synthesized in ER, nascent BACE1 is transiently/reversibly acetylated in seven lysine residues (Lys-126, Lys-275, Lys-279, Lys-285, Lys-299, Lys-300, and Lys-307) in the lumen of the endoplasmic reticulum (ER) by two ER-based acetyl-CoA: ATase1 and ATase2. Acetylation of BACE1 affect its intracellular trafficking [70, 71]. When BACE1 is transported to Golgi apparatus, acetylated BACE1 will be further processed, while non-acetylated BACE1 will be degraded. Studies show that the ability of nascent BACE1 to complete maturation is tightly regulated by ER-based ATases. Indeed, it is only that acetylated intermediates of nascent BACE1 are able to reach the Golgi apparatus and complete maturation, and with the acetyl groups been removed by Golgi-based deacetylase for following post-translational modifications, ceramide regulates both efficiency of acetylation in the ER and rate of deacetylation in the Golgi apparatus [72]. The non-acetylated intermediates are retained in ER or degraded in Golgi apparatus via a process that involves the serine protease PCSK9/NARC-1 [73]. Consistently, it is found that ATase1 and ATase2 are expressed in neurons, and are up-regulated in the brains of AD patients. Studies have shown that up-regulation of ATase1 and ATase2 can elevate the levels of BACE1 and Aβ generation in H4 and SH-SY5Y cell lines [71].

4.2. Glycosylation

O-glycosylation and N-glycosylation are two types of glycosylation that can influence a diverse range of protein properties such as folding, stability, enzyme activity, *etc.* [74]. Glycosylation of BACE1 occurs after being released from the ER to the cytoplasm, where BACE1 is glycosylated to generate a 75-kDa mature BACE1 on the way from ER to Golgi, where fully glycosylated BACE1 protein is produced [75-76]. Glycosylation modification of BACE1 occurs more at N-glycosylation rather than insignificant O-glycosylation [77]. The maturation processes are initiated with an O-glycosylation at sites of Glu46 and further matured with complex N-glycosylation at four Asn-residues in the ectodomain of BACE1 (Asn153, Asn172, Asn223, and Asn354). It is necessary for the disulphide bonds in the catalytic exoplasmic domain to be fully glycosylated and to have the function for the cleavage of APP [78-80]. It is well known that BACE1 is glycosylated with bisecting N-acetylglucosamine (GlcNAc), and research demonstrates that AD

patients have higher levels of bisecting GlcNAc modifications on BACE1, too [78]. Analysis of knockout mice lacking the biosynthetic enzyme for bisecting GlcNAc revealed that cleavage of Aβ-precursor protein (APP) by BACE1 is reduced in these mice, resulting in a decrease in Aβ plaques and improved cognitive function [78]. This modification catalyzed by a GlcNAc transferase Gnt-III is up-regulated in oxidative stress brain and results in the blocking of the lysosomal degradation of BACE1, and elevates the activity of BACE1, leading to increase Aβ generation and plaque formation [81, 82].

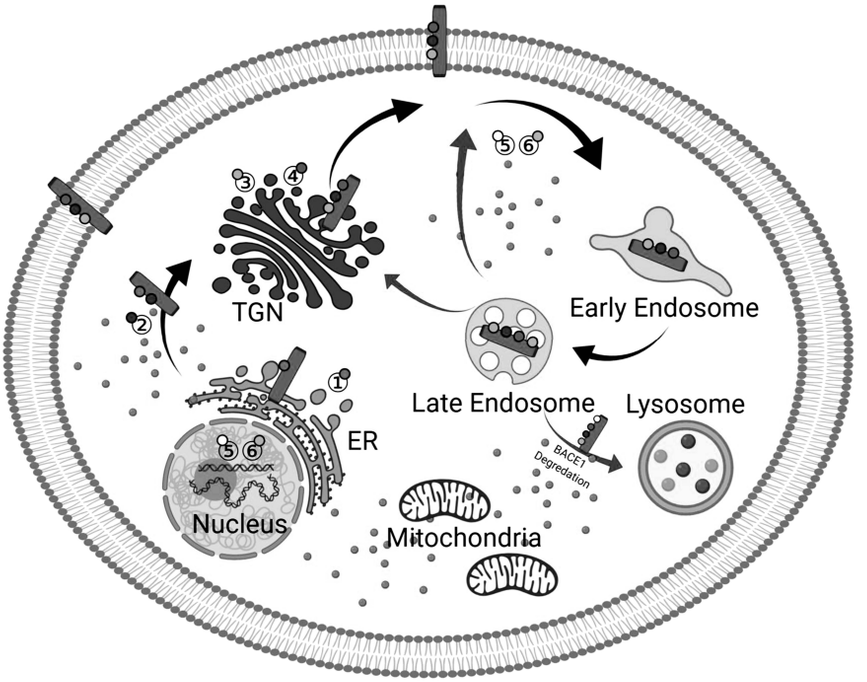

Fig. (3). Mature BACE1 is transported from ER to TGN, and the cell surface, then it is endocytosed in the early and late endosomes (Black arrow). Next, BACE1 can be recycled back to the cell surface, or transited to the lysosome for degradation, or go back to the TGN to be repaired and trafficked back to the cell surface (Red arrow). ① Nascent BACE1 is acetylated in the ER in seven lysine residues, which are important for its catalytic activity and will be deacetylated on Golgi apparatus. The acetylated BACE1 will be further transported to Golgi apparatus to be processed; ② BACE1 is Glycosylated at four Asn-residues after being released from the ER to the cytoplasm to create a 75-kDa BACE1, which affects the maturation of BACE1; ③ BACE1 is palmitoylation on Golgi apparatus at four cysteine residues, which affect the degradation of BACE1 and affects the activity of BACE1; ④ BACE1 is phosphorylated on Golgi apparatus at Ser498 and Thr252, Ser498 influence the subcellular localization of BACE1, while the Thr252 increases the activity of BACE1; ⑤ BACE1 can be ubiquitinated in the cytoplasm and nucleus at three lysine residues, to affect the activity of BACE1 and promote the degradation of BACE1; ⑥ BACE1 can be SUMOylated in the cytoplasm and nucleus at two lysine residues, to affect the activity of BACE1 and prevent the degradation of BACE1. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

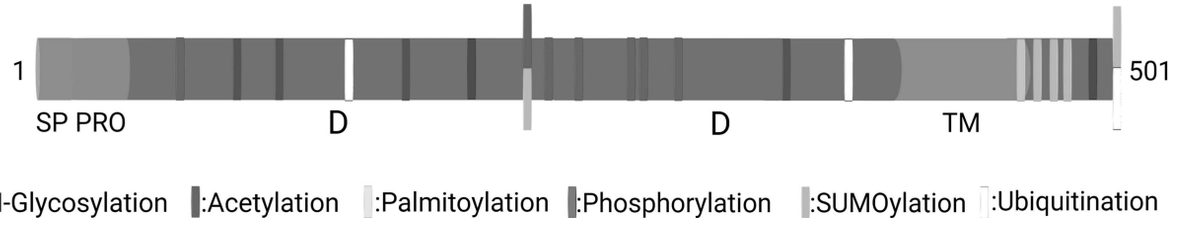

Fig. (4). Post-translational modifications of BACE1. BACE1 undergoes various modifications, including N-glycosylation (N-gly-Asp153, Asp172, Asp223, and Asp354), phosphorylation (P-Ser498, Thr252), acetylation (Acetyl-Lys126, Lys275, Lys279, Lys285, Lys299, Lys300, and Lys307), palmitoylation (Pal-Cys474, Cys478, Cys482, Cys485), SUMOylation (SUMO-Lys275, Lys501), and ubiquitination (Ub-Lys203, Lys382, and Lys501).
Abbreviation: D: two aspartic protease-active sites; SP: signal peptide; Pro: pro-peptide; TM: transmembrane domain. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4.3. Palmitoylation

Protein palmitoylation modifications is an important, pervasive and reversible post-translational modification in eukaryotes with a wide range of biological effects such as modulating protein stability, trafficking, activity, as well as protein-protein and membrane-protein associations [83, 84]. BACE1 is palmitoylated at four juxtamembrane cysteine residues (Cys474, Cys478, Cys482, and Cys485) within its transmembrane/cytosolic tail in Golgi apparatus. Due to the high affinity of acyl chains for the ordered lipid environment, palmitoylated BACE1 can target a variety of peripheral and integral membrane proteins to lipid rafts in nonneuronal cells and in neurons in order to reduce the shedding of BACE1 in the Golgi body [85-87].

Multiple lines of evidence indicate that lipid rafts are involved in amyloidogenic processing of APP, because APP and BACE1 come into immediate contact within this compartment [88-91]. Palmitoylation of BACE1 cytosolic tail Cys residues reduces the shedding of a soluble form of BACE1 from lipid rafts. In the presence of BACE1, intracellular C99 production is enhanced and Aβ is secreted, which means palmitoylation of BACE1 increased Aβ burden in the brain [92]. Displacement of BACE1 by abolishing palmitoylation neither affected the BACE1 cleaving of APP nor the production of Aβ in neurons [85]. A significant reduction of cerebral insoluble amyloid is induced by dystrophic neurites of the absence of BACE1 palmitoylation in 4CA-PDAPP transgenic mouse models, and the lack of BACE1 palmitoylation also improved cognition functions in this mouse model [85, 93]. In addition, it is efficient to change amyloid by modulating BACE1 targeting to dendritic spines and transporting to neurons, instead of affecting BACE1 stability, maturation, or the enzymatic processing of BACE1 and APP [83, 86, 90], which means inhibiting the shedding of BACE1 may be an alternative strategy in the treatment of AD.

4.4. Phosphorylation

Phosphorylation is a reversible process of protein regulation, and it is extremely important in most cellular functions such as protein synthesis, cell division, and signal transduction [94]. Phosphorylation works addition of a phosphate group (PO_4) to the polar group R of various amino acids with the help of protein kinases. After maturation, BACE1 is reinternalized from the cell surface and trafficked between the cell surface and endosomes, then recycle back to the cell surface [95]. In 2001, Walter *et al.* first found that CK-1 can phosphorylate BACE1 at the phosphorylation site Ser498. Full maturation of BACE1 needs phosphorylation at Ser498 in its cytoplasmic domain and at the Thr252 residue in the lumen of endosomes [96]. The former affects the subcellular localization of BACE1, while the letter increases the activity of BACE1 [96-97]. In addition to regulating the retrieval of BACE1 from endosomes vesicles and relocated to Golgi compartments, the phosphorylation of BACE1 at Ser498 can influence the binding of BACE1 to some regulatory proteins such as GGA proteins at the endosomes, particularly, GGA1 [98, 99]. The mechanism is that the phosphorylation of BACE1 at Ser498 increases the combination of BACE1 with GGA by elevating hydrogen bonding and electrostatic interactions and modulates BACE1 retrieval from the endosome to Golgi. Phosphorylated BACE1 interacts with GGA1 in the Golgi to prevent the recycling of BACE1 to the cell surface, where BACE1 cleaves APP, indirectly affecting the production of Aβ [100, 101]. It is reported that there was a three-fold reduction in Aβ production in CHO cells which stably express both APP and the Ser498 phosphorylation [102]. And a significant decrease in the Ser498 phosphorylation of BACE1 in AD patients has also been reported [97].

Interestingly, BACE1 phosphorylation at Thr252 increases the activity of BACE1, which appears to favor the amyloidogenic processing of APP. BACE1 is phosphorylated at Thr252 by p25/Cdk5, and the phosphorylated BACE1 enhances the BACE1 activity by around 27% and increases Aβ levels by 77% in HEK293 cell, further leading to accelerated AD pathology. This process can be inhibited by PPARγ agonist pioglitazone, hence, p25/Cdk5 may represent a promising drug target for the treatment of AD [96, 103].

4.5. Ubiquitination

The ubiquitin-proteasome system is a major protein degradation pathway in eukaryotic cells, to regulates multiple critical cellular functions, including differentiation, proliferation, and apoptosis [104]. After polyubiquitin chain is covalently conjugated to lysine residues of the targeted protein, the ubiquitinated protein will be recognized and transported to the 26S proteasome, and subsequently degraded by lysosome. BACE1 protein can be ubiquitinated at Lys203, Lys382, and Lys501, and GGA3 mediates targeting of BACE1 to the lysosomes for degradation [68-69]. Blocking the ubiquitin-proteasomal pathway inhibits BACE1 degradation, and leads to increased BACE1 enzymatic activity and more β-cleavage product C99 and increases both Aβ40 and Aβ42 production in both neuronal and non-neuronal cells. In all, ubiquitin-proteasome pathway dysregulation might constitute an important event in the pathogenesis of certain AD [101, 105, 106].

4.6. SUMOylation

Protein SUMOylation is covalently attaching the small ubiquitin-like modifing (SUMO) proteins to specific lysine residues in target proteins, to regulate many aspects of normal protein function, such as interactions, subcellular localization, activity, stability, and partnering [107]. BACE1 is SUMOylated at Lys501 and Lys257 residue, predominantly at Lys501 residue, to mediates its intracellular trafficking. SUMOylated BACE1 is mostly localized in the endosomes and transferred to cell membrane to cleave APP, while non-SUMOylated BACE1 is prone to be transported to the lysosomes for degradation. In other words, SUMOylated BACE1 increases its protease activity and stability and subsequently increases in Aβ production, resulting in senile plaque formation and cognitive defect. SUMO/deSUMOyla-

Table 1. Post-translational modifications observed for BACE1.

Feature of PTM	Site	Function	References
Acetylation	Lys-126, Lys-275, Lys-279, Lys-285, Lys-299, Lys-300, Lys-307	Stability; Transit from ER; Intracellular trafficking	[71]
N-Glycosylation	Asp153, Asp172, Asp223 Asp354	Folding; Lysosomal targeting; Rescue degradation	[75 78, 81]
Palmitoylation	Cys474, Cys478, Cys482, Cys485	Target to and reduces shedding from lipid rafts	[77, 87, 92]
Phosphorylation	Ser498, Thr252;	Endosomal-lysosomal trafficking; Enhancement of activity	[95-96]
Ubiquitination	Lys203, Lys382, Lys501	Degradation	[69]
SUMOylation	Lys275, Lys501	Stability, Intracellular trafficking, Escalates activity	[110]

tion imbalance of BACE1 and tau can be found in the early phases of AD, and contribute to loss of synapse [108, 109]. Besides, compared with a non-SUMOylated mutant, injection of wild-type BACE1 significantly increase Aβ production and triggers cognitive dysfunction in APP/PS1 AD mice [110]. These data suggest that inhibition of Lys501 SUMOylation on BACE1 may be a beneficial potential therapeutic target for AD.

CONCLUSION AND FUTURE DIRECTIONS

Accumulating evidence suggests that AβO may be more likely to act as a trigger than a result of AD and other neurodegenerative diseases. AβO may be less important or even irrelevant to the later stage of the disease, so reducing the early production of Aβ is the key point to prevent and alleviate AD. Given that BACE1 is a crucial molecule of Aβ production, inhibition drugs of BACE1 function were almost wiped out in recent years, partly due to complications related to the physiological function of BACE1. BACE1 gene knockout experiments have offered insight into the physiological functions of BACE1 and warned of the risks associated with total eradication of its activity.

The post-translational modification of BACE1 mostly affects the maturation and transportation of BACE1 rather than directly affecting its activity Table (**1**), which means post-translation modification of BACE1 could be a promising new drug discovery strategy. In this paper, recent studies were reviewed about Aβ and AD pathogenesis, toxicity of AβO, and BACE1 and AβO, especially in the post-translational modification of BACE1. We systematically summarized and evaluated that the relationship between different post-translational modifications of BACE1 (Acetylation, Glycosylation, Palmitoylation, Phosphorylation, Ubiquitination and SUMOylation) and Aβ generation, maturation and degradation. Discovering the novel drugs, including naturally active molecules, on the basis of the post-translational modification of BACE1 should be one of the prospective therapeutic strategies for treatment AD in the future.

We checked the relevant literature to find out if there are any compounds that have a clear effect on the post-translational modification of BACE1. Unfortunately, only three compounds have been clearly reported on the post-translational modification of BACE1 (lovastatin, simvastatin and licoflavonol, details are showed in Table S1), and we cannot in depth discuss drug targeting to post translational regulation of BACE1. But there are many studies on the effects of BACE1 expression, activity, and search inhibitors based on the structure of BACE1(some has been used for commercialization). It is not clear whether these compounds have any effects on the post-translational modification of BACE1. Here, we gathered the compounds that regulate BACE1 in the literature, which can be used for subsequent research on whether BACE1 is a post-translationally modified compound library [Table S2-S5].

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
Aβ	=	Beta Amyloid
APP	=	Amyloid Precursor Protein
BACE1	=	β-secretase 1
CSF	=	Cerebrospinal Fluid
AMP	=	antimicrobial Peptides
AβO	=	soluble amyloid-β Oligomers
CNS	=	Central Nervous System
ER	=	Endoplasmic Reticulum
C99	=	Carboxy-terminal Fragment 99
Cys	=	Cysteine
Ser	=	Serine
Thr	=	Threonine
Asn	=	Asparagine
Lys	=	Lysine

AUTHORS' CONTRIBUTIONS

SJX conceived, planned, critically reviewed, edited, and revised the paper; WW, PL and PWL planned, wrote the original manuscript, edited manuscript and visualization; FSW critically revised the final manuscript. JHH contributed significantly to the manuscript preparation and revision of the manuscript.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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