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Critical Review

Transcriptional and Post-transcriptional Regulation of β-Secretase

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Summary

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that results in loss of memory and cognitive function, eventually leading to dementia. A key neuropathological event in AD is the cerebral accumulation of senile plaques formed by aggregates of amyloid-β-peptides (Aβ). Aβ results from two sequential endoproteolytic cleavages operated on the amyloid-β precursor protein (AβPP), an integral membrane protein with a single-membrane spanning domain, a large extracellular N-terminus and a shorter, cytoplasmic C-terminus. First, β-secretase (BACE1) cleaves AβPP at the N-terminal end of the Aβ sequence to produce a secreted form of AβPP, named sAβPP, and a C-terminal membrane-bound 99-aminoacid fragment (C99). Then, γ-secretase cleaves C99 within the transmembrane domain to release the Aβ peptides of different lengths, predominantly Aβ1-40 and Aβ1-42.
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The expression and the enzymatic activity of β-secretase (BACE1) are increased in the brains of Alzheimer's disease (AD) patients. Moreover, age-related stress may increase BACE1 levels and drive AD pathogenesis. The precise mechanisms of this upregulation are not completely understood; here, we discuss the relevance of a number of recently identified transcription factors as well as post-transcriptional modifications and activation of intracellular signaling molecules for the regulation of BACE1 expression in the brain.

BACE1 STRUCTURE

The BACE1 gene encodes for a protein of 501 amino acids (*1–5*) consisting of an N-terminal signal peptide (residues, 1–21), followed by a prodomain (residues, 22–45), a protease domain (residues, 46–460) which contains two consensus motif characteristic of an aspartyl protease active site (DTGS, at residues 93–96, and DSGT, at residues 289–292), a single transmembrane domain (residues, 461–477), and a short cytosolic domain (residues, 478–501).

The crystal structure of BACE1 is complex and the enzyme's active site is larger and less hydrophobic than that of other human aspartic proteases (*6*), making it a difficult target for designing inhibitors (*7*). A distinctive feature of BACE1 is its anchoring in the membrane through a single-transmembrane domain, which allows the placement of its catalytic domain in the same orientation as APP (*8*). At an optimal pH of 4.0–5.5, BACE1 is expected to operate in acidic intracellular compartments such as the trans-Golgi network, endosomes, and lysosomes (*2, 3, 5*).

BACE1 full maturation involves various post-translational modifications. Analysis of its primary sequence revealed four sites of *N*-glycosylation within the protease domain (Asn residues 153, 172, 223, and 354), as confirmed by site-directed mutagenesis experiments (*9, 10*). BACE1 undergoes cotranslational *N*-glycosylation in the ER, as demonstrated by treatment with tunicamycin, which inhibits the first step of glycoprotein synthesis.

Further complex glycosylation is achieved as BACE1 transits through the Golgi (*11*). There is evidence that sulfation can also occur on the *N*-glycosylation sites as part of BACE1 maturation (*12*). Depending on experimental conditions and individual cell lines' glycosylation machinery, the molecular weight of BACE1 has been reported to be between 70 and 75 kDa for the mature protein (*8, 9, 11, 13*), and between 60 and 70 kDa for its immature forms (*8, 9, 11, 13*). The carbohydrate content of BACE1 accounts for about 30% of its molecular weight, similar to other endosomal/lysosomal resident proteins.

BACE1 and the Pathogenesis of Sporadic and Familial AD

The majority of AD cases are sporadic with late onset and no defined cause. Several reports show increased levels and

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activity of BACE1 protein in the brain of sporadic AD patients, compared to normal age controls (*14–16*). Oxidative stress (OS) is potentially involved in the pathogenesis of sporadic AD as it is correlated with age as much as AD (*17*). More causally, OS and Aβ are interconnected to each other as Aβ induces OS (*18*) and OS in turn increases the production of Aβ (*19*).

We have proposed a sequence of events that link OS, BACE1 induction, and apoptotic cell death mediated by an overproduction of Aβ1-42. First, we have shown that oxidant agents and 4-hydroxynonenal significantly increase the expression, protein levels, and activity of BACE1 in NT2 neurons (*20, 21*). These events are followed by both an overproduction of Aβ peptides and morphological signs of apoptotic cell death (*22*). Then, we have found that OS increases the γ-secretase activity both *in vitro* and *in vivo*, and that the increased BACE1 expression induced by OS is regulated by the γ-secretase activity (*23*). These results have important implications for the pathogenesis of sporadic AD. First, they suggest that OS, secondary to different AD risk factors, can increase the expression of both secretases, thereby enhancing Aβ production. Second, our data revealed the existence of a positive feedback loop in which the γ-secretase activity regulates BACE1 expression, a finding confirmed by Jo et al. (*24*).

A strong inflammatory reaction is present in AD brain, and long-term nonsteroidal anti-inflammatory drugs (NSAID) use reduces the risk of AD, suggesting that inflammation may play an important role in AD pathophysiology (*25*).

In fact, the BACE1 promoter also bears a binding site for the transcriptional regulator proliferator-activated receptor γ (PPARγ) (*26*). Activation of PPARγa by NSAIDs or PPARγ agonists causes repression of BACE1 gene promoter activity, whereas proinflammatory cytokines that reduce PPARγc levels lead to increased BACE1 mRNA (*26*).

The activity of BACE1 is increased also in the familial early onset AD (FAD). We showed that PS1 mutations increase BACE1expression and that this effect is dependent on the presence of APP and is proportional to the amount of Aβ1-42 produced and secreted in the extracellular milieu (*27*). This novel effect of PS1 mutations implies the existence of a positive feedback loop from the γ- to the BACE1 cleavages of APP in which Aβ1-42 is the APP derivative that influences/modulates BACE1 transcription through the activation of the c-Jun NH2-terminal kinase (JNK)/AP1 cascade (*28*). PS1 mutations result in a wide and heterogeneous clinical phenotype that includes atypical presentations, such as ataxia, paraparesis, and epilepsy (*29–31*). The upregulation of BACE1 determined by PS1 mutations may contribute to determine FAD phenotype. Indeed, the overexpression of BACE1 increases the production of N-terminal-truncated Aβ species (*32*). We and others (*33*) have shown that the composition of soluble Aβ reflects the pathological and clinical phenotype of Aβ amyloidosis and that the prevalence of N-terminal-truncated Aβ1-42 peptides correlates with the rate of aggregation and with the degree of toxicity of the mixture of Aβ species (*34*). Moreover, recent data obtained with different animal models of Aβ amyloidosis support the hypothesis that the composition of Aβ species, indicated as "Aβ strains" (*35–37*), dictates the conformation of Aβ-soluble aggregates, which in turn produces different pathological phenotypes. The mechanisms of BACE1 upregulation vary from transcriptional, post-transcriptional, translational, post-translational, and degradation control.

Transcriptional Control of BACE1

The human BACE1 gene spans approximately 30 kb on chromosome 11q23.2 and includes nine exons. BACE1 gene promoter has a complex structure, divided into two distinct promoter regions, carrying several transcription actor-binding sites, many of which are organized in repeats, typical of an inducible protein (*38*).

Different signaling pathways and transcription factors, such as sp1, NF-κB, JNK/AP-1, hypoxia inducible factor 1 (HIF-1)α, and p25/cdk55/STAT3 have been suggested to control BACE1 transcription.

Sp1. One of the first studies that provides information about the molecular mechanism regulating BACE1 gene expression came from Christensen and collaborators (2004) and showed that the transcription factor sp1 plays a significant role in this regulation: sp1 overexpression facilitates BACE1 promoter activity, whereas lack of endogenous sp1 protein in sp1-KO cells markedly reduces the transcriptional activation of BACE1 gene (*39*). The relevance of this study was recently confirmed by a completely different experimental approach. Prenatal lead exposure in rats induces a robust and long-lasting increase in Sp1 expression which results in increased APP mRNA and protein BACE1 expression and Aβ generation (*40*). Thus, sp1 is involved in amyloidogenesis by a concurrent activation of APP and BACE1 expression.

The crucial role of sp1 in regulation of BACE1 was recently supported by the finding that molecules able to decrease Aβ production interfere with sp1 transcriptional pathway (*41*). These findings demonstrate that interference with sp1 transcriptional pathways can lower pathogenic intermediates associated with AD.

On the other hand, 12/15-lipoxygenase, an enzyme widely distributed in the central nervous system, increases the amyloidogenic processing of APP through a sp1-mediated transcriptional control of BACE1 levels (*42*).

NF-κB. Another transcription factor that plays a role in AD pathogenesis by regulating BACE1 levels is NF-κB. The suppressor role of NF-κB is supported indirectly by the evidence that the lipid peroxidation product 4-hydroxynonenal inhibits both constitutive and inducible NF-κB activities (*43*) and increases BACE1 expression (*20, 22*).

Moreover, in addition to suppress BACE1 expression, the NF-κB signaling pathway is one of the major neuroprotective

pathways in AD (*44*). Treatment of neuronal cells with low, nontoxic Aβ peptide concentrations induces NF-κB activation (*45*) and leads to neuroprotection against subsequent treatment with toxically high Aβ peptide concentrations (*46*). Vice versa, the IκB kinase inhibitor, BMS345541, that completely blocks NF-κB transcriptional activity, fully reverses the Aβ1-42-induced increase of BACE1 promoter transactivation (*47*).

We recently demonstrated a novel pathogenetic mechanism involving the advanced glycated end-products (AGEs), which contributes to Aβ accumulation (*48*). In streptozotocin diabetic rats, as well as in SK-N-BE-differentiated neuroblastoma cells, two different AGEs, pentosidine and glyceraldehyde-derived pyridinium, were able to upregulate BACE1 expression through their binding with the receptor of advanced glucation products (RAGE). The binding was followed by a strong production of reactive oxygen species (ROS) and by an activation of the NF-κB pathway, which is known to be activated by RAGE (*49*). In this context, it has been recently reported that minocycline, a potential neuroprotective tetracycline derivative (*50*), downregulates BACE1 expression and thus Aβ accumulation in the hippocampus of diabetic mice inhibiting NF-κB pathway activation (*51*).

Moreover, other different compounds lower BACE1 activity through the inhibition of NF-κB pathway, as described recently (*52, 53*), suggesting that this pathway could be a useful therapeutic target.

Altogether, these data indicate that NF-κB regulation of BACE1 transcription may be altered in AD owing to chronic stress. The failure in the transcriptional regulation by NF-κB of BACE1 may in part account for increased BACE1 transcription and subsequent amyloidogenic APP processing in a cell type-specific manner. The functional NF-κB site in the BACE1 promoter is stimulatory in activated astrocytes and Aβ-exposed neuronal cells and repressive in neuronal and quiescent astrocytic cells.

Finally, it has been recently found that NF-κB differentially regulates Aβ production at physiological and supraphysiological Aβ concentrations by modulating transactivation of βAPP and secretase promoters. Thus, under physiological conditions, NF-κB regulates Aβ homeostasis, whereas it contributes in increasing Aβ production in the pathological context (*54*).

It is thus possible that BACE1, given its complex promoter structure and its relationships with heterogeneous signaling pathways (*38, 47, 55*), can be part of a pool of enzymes that respond to cellular stress or homeostasis modifications. As in the case of glucose lowering signals, where insulin and metformin have opposite effects on amyloidogenesis and BACE1 regulation (*56*), in some pathways the same endpoint can result in opposite outcomes on BACE1 activation. This may be owing to the fact that BACE1 is working together with still undefined partners to fulfill a cellular response.

HIF-1α. Although AD is classified as a neurodegenerative dementia, there is epidemiologic and pathologic evidence of an association with vascular risk factors and vascular disease (*57*) with which AD could share pathogenetic mechanisms. Cerebral hypoperfusion and hypoxia trigger hypometabolic, cognitive, and degenerative changes in the brain and contributes to the pathologic process of AD (*58*).

Indeed, hypoxia increases the expression and activity of BACE1, as shown *in vitro* as well as in AD transgenic model (*59, 60*). One proposed mechanism of the effect of hypoxia on BACE1 upregulation is that the activation of hypoxia inducible factor 1 (HIF-1), a transcription factor that regulates oxygen homeostasis, binds to BACE1 promoter, and regulates its gene expression (*60*). We more recently extended these findings, showing both *in vivo* and *in vitro* that hypoxia upregulate BACE1 mRNA expression in a biphasic manner, through two distinct mechanisms: 1) an early release of ROS from mitochondria and 2) a late activation of HIF-1α (*61*).

The early posthypoxic upregulation of BACE1 recapitulates the cascade of events induced by oxidant agents: an increase of BACE1 expression and activity, whereas chronic hypoxia triggers the second mechanism of BACE1 upregulation, HIF-1α activation.

HIF-1α seems to be the pathway link between cerebrovascular dysfunctions and AD. It has been recently observed that, in rat brain capillary endothelial cells, oxygen glucose deprivation treatment elicits a strong production of Aβ1-42 peptide through a mechanism that involves the HIF-1-mediated BACE1 upregulation (*62*). The inhibition of the HIF-1α pathway could provide a new insight into prevention and treatment of AD. It is worth noting that salidroside, a compound extracted from the root of *Rhodiola rosea*, which has been used in traditional Tibetan medicine since long ago, is able to attenuate abnormal processing of amyloid precursor protein induced by hypoxia in SH-SY5Y cells, decreasing BACE1 expression and protein levels of HIF-1α (*63*).

AP1/JNK. The upregulation of BACE1, induced by OS, requires the activation of JNK-AP1 pathway (*22*). This pathway is activated in AD brain (*64–66*), to respond to cell stress and to mediate apoptosis (*67–70*). Moreover, JNK activation is associated with age-dependent amyloid plaque deposition, tau phosphorylation, and the loss of synaptophysin in a Tg2576/PS1 double transgenic mice (*71–73*). We and others have also discovered that BACE1 activation is regulated by the γ-secretase activity, and requires the activation of JNK-AP1 pathway (*23, 25*). Then, we have found that Aβ1-42 is the product of the γ-secretase cleavage that upregulates BACE1 expression (*23, 27*) and that Aβ1-42 increases BACE1 gene transcription through the activation of JNK/c-jun signaling pathway (*28*). Although the mechanisms of JNK activation by Aβ1-42 remain unclear, it is likely that JNK is activated by Aβ1-42 indirectly, perhaps by the interaction of Aβ1-42 with yet unidentified receptors. Indeed, different proteins, such as APP itself, NMDA, TrkA, and LRP family of receptors, interact with Aβ peptides (*74, 75*). This could lead not only to BACE1 regulation but also to

the control of a pool of genes involved in a specific cellular function. The knowledge of the genes activated by Aβ may be determinant to understanding the precise series of events, leading to neuronal dysfunction and degeneration in AD.

Post-transcriptional Control of BACE1

Additional nontranscriptional mechanisms have been hypothesized to account for increased BACE1 protein levels and activity.

BACE-1 translation is regulated at multiple stages, consistent with the presence of a long and highly conserved transcript leader (*76, 77*). In particular, the 5′-UTR represses the rate of BACE1 translation (*78*), and alternative splicing of the transcript leader can influence the rate of translation in a tissue-dependent manner (*76*). A detailed mutagenesis analysis suggested that the GC-rich region of the 5′-UTR acts as a "translation barrier" (*78*). The presence of several upstream ATGs also strongly reduces the translation of the main open reading frame, which implies that BACE1 translation might increase in conditions that favor phosphorylation of the translation eukaryotic initiation factor-2a (eIF2a) (*76*). More recent studies have shown that cellular energy deprivation (glucose deprivation in cell culture) produces a post-transcriptional increase in BACE1 levels, which is indeed mediated through increased eIF2a phosphorylation (*78*). These observations *in vitro* correlated with *in vivo* studies in AD transgenic (Tg2576) mice, in which chronic energy inhibition with 2-deoxyglucose or 3-nitropropionic acid was shown to increase eIF2a phosphorylation, BACE1 levels, and amyloidogenesis (*79*). A BACE1 protein stability can also be influenced by the lysosomal pathway (*80*). Tesco and colleagues (*81*) have demonstrated that lysosomal but not proteosomal inhibitors lead to the accumulation of both endogenous and ectopically expressed BACE1 in a variety of cell types including primary cortical neurons. Moreover, it has been shown that BACE1 accumulates in late endosomes/lysosomes after inhibition of lysosomal hydrolases, indicating that BACE1 is transported in late endosomes/lysosomes where it can be degraded via the lysosomal pathway.

Intriguingly, GGA (Golgi-localized γ-ear-containing ARF-binding proteins) 1, 2, and 3, involved in the transport from the Golgi complex to the endosomes of proteins containing the DXXLL signal have been shown to bind the BACE1 acidic dileucine motif (*82*). Moreover, phosphorylation of serine 498 in BACE1 increases their binding (*83*). Also, the downregulation of GGAs significantly increases the levels of BACE1 in endosomes and GGAs may be necessary for BACE1 transport back to trans Golgi (*84*).

More recently, it has been shown that GGA3, unexpectedly, regulates levels and activity of BACE1 by interaction with ubiquitin and not via di-leucine motif (*85*), thus a GGA3 mutant with reduced ability to bind ubiquitin is unable to regulate BACE1 levels and activity. These findings are in agreement with increasing evidence, showing that GGAs bind ubiquitin and traffic both synthetic and endosomal ubiquitinated proteins to lysosomes (*86, 87*). As levels of BACE1 are elevated in AD brains and they are inversely correlated with GGA3 levels (*85*), these studies suggest that therapies able to increase GGA3 expression in the brain may represent a potential treatment for AD.

In addition to GGAs, reticulons, a novel gene family that were shown to participate in all apoptosis signaling pathways, may be novel players in AD pathogenesis (*88*).

Thus, the reticulon/Nogo has been shown to interact with BACE1 and regulate its activity (*89*). Moreover, the overexpression of reticulon 3 (RTN3) also results in the retention of BACE1 in the endoplasmic reticulum and the reduction of Aβ production both *in vivo* and *in vitro* (*90*).

Additional post-transcriptional mechanisms have been suggested to lead to increased BACE1 protein levels and activity. It has been found that the expression of BACE1 antisense transcripts, which respond to cellular stresses and to Aβ itself, stabilizes BACE1 mRNA (*91*); moreover, alternative splicing of BACE1 pre-mRNA acts as a control system as well (*92*).

Aβ1-42 Modulates BACE1 Levels Through Both Transcriptional and Post-transcriptional Mechanisms

It has been suggested that Aβ might play a role not just as a toxic peptide, but also as a functional signaling molecule. The most convincing evidence was obtained from the study of Kamenetz et al. (*93*), showing that Aβ is the player of a negative feedback loop that controls the synaptic activity. These data agree with the finding that Aβ production is proportional to the level of brain activity, as demonstrated in the recovery from severe cranial trauma (*94*).

Gatta et al. (*95*) performed a microarray assay, showing that exposure of neuroblastoma cells to an Aβ1-42-aluminum complex is followed by a selective change in gene expression; the activated genes are involved in the modulation of calcium homeostasis, glutamatergic transmission, OS, inflammation, and apoptosis (*95*).

We showed an induction of BACE1 occurring at low concentrations of monomeric preparations of Aβ1-42 and starting within minutes of treatment (*96*). Although this may seem a short time interval, specific gene transcription can occur within minutes for certain cellular processes (*97*). It is likely that BACE1 is part of a cellular response aimed at fast adaptation to extracellular stimuli.

We have also found that Aβ1-42 downregulates the activity of ubiquitin C-terminal hydrolase L1 (Uch-L1), through the activation of NF-κB pathway, and that this event is associated to an upregulation of BACE1 (Fig. 1) (*98*).

Uch-L1 is an abundant neuronal enzyme, representing 1–2% of total soluble brain proteins (*99*). Uch-L1 has two enzymatic activities. The first one, known as hydrolase, removes and recycles ubiquitin molecules from the degraded proteins. This recycling action is crucial for the degradation process as it gen-

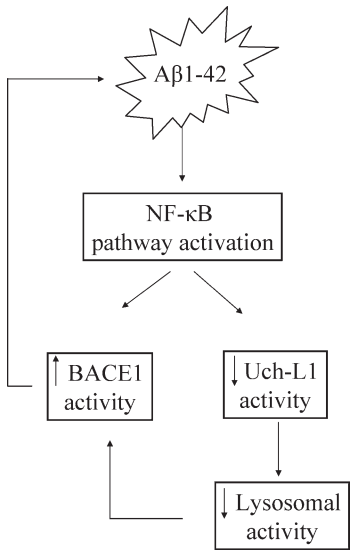

Figure 1. Pathogenetic hypothesis in which Aβ1-42 mediates a BACE1 increase and a parallel Uch-L1 decrease through the activation of NF-κB pathway. The Uch-L1 decrease then further fosters BACE1 activity interfering with its lysosomal degradation through a post-transcriptional mechanism.

erates free monomeric ubiquitin which can be reused for further reactions of ubiquitination (*100*). The second one, called ubiquitin ligase, links ubiquitin molecules, thus generating polyubiquitine chains that tag proteins for disposal. To play this activity, the enzyme has to be dimerized *in vitro* and remains unclear whether this activity also occurs *in vivo* (*100*). Several lines of evidence suggest a possible link between Uch-L1 activity and AD: the activity of Uch-L1 is downregulated in AD brain (*101, 102*) and its levels are inversely proportional to the number of neurofibrillary tangles in the brains of sporadic AD patients (*102*).

Moreover, Aβ increases in spontaneous neurological mutant with axonal dystrophy in the gracile tract of the medulla oblongata and spinal cord of mice lacking Uch-L1 expression (*103*). In a mouse model of AD, the double transgenic mouse overexpressing APP together with mutant presenilin 1 (APP/PS1 mice), the Uch-L1 protein expression, and activity in brain are also decreased (*104*). Downregulation of Uch-L1 seems to be at least in part responsible for the impairment of long-term potentiation (LTP) (*105*). The effect of Aβ on LTP is mediated by the inhibition of phosphorylation of the cAMP response element-binding protein (CREB), a transcription factor activated by cAMP-dependent protein kinase A (PKA) (*106*). The inhibition of Uch-L1 activity would lead to impairment of the degradation of the PKA regulatory subunit, a decrease in its activity, and subsequently downregulation of CREB-dependent transcription (*104*).

The correlation between the inhibition of Uch-L1 and the upregulation of BACE1 was previously reported by Zhang et al. (*107*), who showed that inhibition of Uch-L1 significantly increases BACE1 protein levels in a time-dependent manner. Moreover, overexpression of Uch-L1 decreased APP c-terminal fragment C99 and Aβ in the Uch-L1-null AD mice (*107*).

We extended these findings, showing that the decrease of Uch-L1 activity is related with the Aβ1-42-mediated activation of NF-κB pathway (*98*). Recently, the Uch-L1 gene promoter region was cloned and functionally identified, and a NF-κB-binding element within its promoter region identified. NF-κB signaling downregulates Uch-L1 expression and mediates the inhibitory effect of lipopolysaccharide and tumor necrosis factor-α (TNF-α) on Uch-L1 expression (*108*).

We next demonstrated that these effects were not only concomitant but also that the decrease in Uch-L1 rebounded on BACE1 degradation (*98*).

Thus, our data indicate that BACE1 is transported in the late endosomal/lysosomal compartment where it is degraded via the lysosomal pathway (*81*), and not in the proteosome.

The involvement of lysosomal pathway in BACE1 degradation was confirmed by three findings. 1) Treatment of cells with lysosomal inhibitors was followed by a significant accumulation of BACE1. 2) Confocal laser scanner microscopy demonstrated that BACE1 colocalizes with the lysosome marker LAMP-1. 3) We have determined that BACE1 is Lys-63-linked ubiquitinated. Kang et al. (*85*) previously reported a lys-63-linked ubiquitination of BACE1, showing that GGA3 regulates the BACE1 degradation via the interaction with ubiquitin. In this scenario, loss of functional Uch-L1 could lead to inadequate ubiquitination of BACE1 mediated by a decrease in free ubiquitin.

Finally, we found that the Uch-L1 inhibitor LDN-57444 as well as Aβ1-42 impairs the activity of cathepsin D, considered a marker of lysosomal activity (*98*).

Lysosomal dysfunction has been linked to a spectrum of degenerative diseases (*109*), many of which involve the CNS (*110*). Alterations of the endosome/lysosome system have also been previously described in AD (*111*). It has been shown that BACE1 and Aβ are enriched in lysosome-related autophagic vesicles in APP transgenic mouse models (*112*). The autophagic vesicles accumulate also in dystrophic neuritis in AD brains (*113*).

Thus, our findings described a transcriptional role of Aβ1-42 that mediates the inhibition of Uch-L1 and the upregulation of BACE1 mediated by NF-κB pathway activation and a post-transcriptional mechanism that impairs BACE1 lysosomal degradation (*98*).

CONCLUSIONS

To summarize, protein BACE1, the levels of which are elevated in the brain of sporadic AD patients, is controlled both transcriptionally and post-transcriptionally by molecules which have been recently identified. Different signaling pathways and transcription factors, such as sp1, NF-κB, JNK/AP-1, and p25/cdk55/, HIF-1α 5′-UTR, and p25/cdk55/STAT3 STAT3 influence the rate of BACE1 translation, whereas several upstream

ATGs, eIF2a phosphorylation, GGA3, reticulon/Nogo, and Uch-L1 play a role in post-transcriptional control. All these regulatory molecules represent potential targets for the development of compounds that can interfere with BACE1 expression/activity, to be introduced in the clinic as drugs in the therapy of AD.

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