Biochemical Society Transactions (2024) **52** 2539–2556
https://doi.org/10.1042/BST20241510

Review Article

The AICD interactome: implications in neurodevelopment and neurodegeneration

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The pathophysiological mechanism involving the proteolytic processing of amyloid precursor protein (APP) and the generation of amyloid plaques is of significant interest in research on Alzheimer's disease (AD). The increasing significance of the downstream AD-related pathophysiological mechanisms has sparked research interest in other products of the APP processing cascades, including the APP intracellular domain (AICD). The potential importance of AICD in various cellular processes in the central nervous system has been established through the identification of its interactors. The interaction between AICD and its physiological binding partners is implicated in cellular events including regulation of transcriptional activity, cytoskeletal dynamics, neuronal growth, APP processing and cellular apoptosis. On the contrary, AICD is also implicated in neurodegeneration, which is a potential outcome of the functional fluctuation of AICD-mediated neuronal processes within the neuronal network. In this review, we summarize the neuronal functions and pathological manifestations of the dynamic AICD interaction network.

Introduction to amyloid precursor protein and its intracellular domain

Over the last century, research in Alzheimer's disease (AD) has accumulated a large body of data corroborating the amyloid cascade hypothesis (ACH). ACH posits the extracellular deposition of amyloid-β (Aβ) peptides as the causal agent of AD pathogenesis [1]. Aβ is derived from aberrant proteolysis of the amyloid precursor protein (APP) by β- and γ-secretase sequentially. γ-Secretase-mediated APP cleavage simultaneously releases APP intracellular domain (AICD), a 6-kDa protein fragment, into the cytosol. APP and its closely related mammalian homologues, namely APP-like proteins 1 and 2 (APLP1 and APLP2), are transmembrane proteins which share a conserved structure: a large N-terminal ectoplasmic domain, a single membrane-spanning domain and a small C-terminal cytoplasmic domain [2,3].

APP is a type I transmembrane protein, and such transmembrane proteins, like Notch and low-density lipoprotein receptor protein family (LRP), often function as a cell surface receptor to detect and transduce extracellular signals. For instance, LRP-5 and -6 are involved in Wnt signaling as they are co-receptors to Wnt ligands, that regulate Wnt-mediated cell proliferation[4–6]. Similarly, APP has recently been revealed as a conversed Wnt receptor. CRD of APP on the N-terminal has shown to be the receptor for Wnt ligands, including Wnt5 and Wnt3a, which regulate the expression of APP itself, and also regulate Wnt-mediated neurite development [7]. The extracellular domain of APP is also associated in cell-cell adhesion and synaptic adhesion. X-ray structure confirms the parallel and antiparallel dimerization of APP via its E2 domain [8]. Further research has then revealed the role of APP cis- and trans-dimerization in intercellular adhesion [9]. In addition, since all APP family members are located at pre- and post-synapses, the dimerization of APPs at synapses has been shown to be important for synaptic differentiation and maintenance [10].

Received: 19 September 2024
Revised: 25 November 2024
Accepted: 26 November 2024

Version of Record published:
13 December 2024

Biochemical Society Transactions (2024) **52** 2539–2556
https://doi.org/10.1042/BST20241510

There are eight APP isoforms derived from the alternative splicing of the *APP* gene. APP_{695}, APP_{751} and APP_{770} are the three major mammalian isoforms, with APP_{695} being the major form expressed in the neurons [11,12]. N-terminally, the ectoplasmic domain of APP consists of E1 and E2 domains connected by an acidic domain (AcD). The ectodomain of APP isoforms also contains an Ox-2 antigen domain (Ox-2) in APP_{770} and an kunitz protease inhibitor (KPI) domain, which is present in both APP_{751} and APP_{770}. The E1 domain is composed of a growth-factor-like domain (GFLD), a cysteine-rich domain (CRD) and a copper-binding domain (CuBD) while the E2 domain contains a heparin-binding domain (HBD) and a CuBD. The center of APP is a single-spanning transmembrane helix (TM) connected to the N-terminal ectodomain via the juxtamembrane region (JMR). AICD in the cytosolic domain possesses a highly conserved tyrosine–glutamate–asparagine–proline–threonine–tyrosine (YENPTY) motif through evolution (Figure 1).

Regulated intramembrane proteolysis (RIP) of APP family proteins generates secreted and cytosolic peptides that are associated with distinct functions [2]. APP can be cleaved into two mutually exclusive processing pathways, termed non-amyloidogenic and amyloidogenic pathways (Figure 1). During non-amyloidogenic processing of APP, APP is cleaved by α-secretase to release a soluble ectodomain fragment called secreted APPα (sAPPα) and membrane-bound C-terminal fragment α (CTFα). CTFα is then further processed by γ-secretase to release a non-toxic p3 peptide and AICD [13]. In amyloidogenic processing, APP is subsequently cleaved by β-secretase and γ-secretase to release secreted APPβ (sAPPβ) and membrane-bound C-terminal fragment β (CTFβ) which is further cleaved by γ-secretase to secret AICD and neurotoxic Aβ [13]. AICD is the common fragment released from both non-amyloidogenic and amyloidogenic pathways under physiological conditions. However, the amyloidogenic pathway is more prominent in AD, resulting in increased production of Aβ and AICD, which may lead to pathological consequences. Of note, AICD can be further cleaved by caspases at Asp664, releasing two cytotoxic peptides, C31 and Jcasp (Figure 1). Increasing evidence reveals the biological significance of the aforementioned intracellular cleavage products of APP, particularly AICD. Sequence alignment of AICD proteins produced by APP family members across different species demonstrates the protein contains an absolute conserved YENPTY motif [14]. This motif is recognized by AICD interacting proteins (AIP) which contain a phosphotyrosine-binding (PTB) domain. To note, PTB domains play important roles in cell fate determination, protein targeting and trafficking and tyrosine-kinase modulated signaling cascades. FE65 is one of the first identified AIP which interacts with the YENPTY motif via its PTB domain. The following AIPs were then discovered as they interact with AICD in a similar manner, such as JNK-interacting protein 1 (JIP1), Disabled-1 (Dab1), GULP PTB domain containing engulfment adaptor 1 (GULP1), Numb and X11 family [15–18]. Several interactions between AICD and AIPs have been reported to affect the production of Aβ (Table 1). For example, overexpression of X11α or X11β in AD mouse models expressing APP Swedish mutation (APPswe) remarkably attenuates Aβ plaque deposition [19,20]. Conversely, models deficient of X11β or both X11β and X11α exhibit enhanced level of Aβ in the hippocampus [20,21]. Further studies suggested that the interaction between X11 and APP through AICD facilitates the translocation of APP out of detergent-resistant membrane, where β-secretase is active, and hence prevent amyloidogenic cleavage of APP [21]. This demonstrates the importances of the overall role of APP and its cleavage products, including AICD, in neurodegenerative diseases. Most AIPs are adaptor proteins that lack catalytic domains to possess a direct functional role, however, they all composed of diverse protein-protein interacting domains that allow them to bind with different interacting partners to participate in different cellular mechanisms, both AICD-dependently or -independently.

Physiologically, Aβ is a comparatively minor metabolic product of APP as the majority of APP is processed by α-secretase within the Aβ sequence, thereby prohibiting the production of Aβ. Nevertheless, a shift toward β-secretase processing of APP would increase the production of Aβ, which may contribute to AD pathogenesis, as reviewed elsewhere [22,23]. Notably, there is a significant increase of AICD in the brain of APPswe, a model of the amyloid pathology [24]. Furthermore, in the hippocampus of AD patients, AICD is accumulated in Hirano bodies in dystrophic neurites [25]. Such observation may suggest that AICD also contributes to AD pathogenesis.

Physiological roles of AICD

Gene transcription

AICD is constitutively located in the nucleus [41] where it serves as a transcription factor. Thus, it is suspected that AICD-mediated nuclear signaling can be regulated by the binding of AIP to its evolutionarily conserved

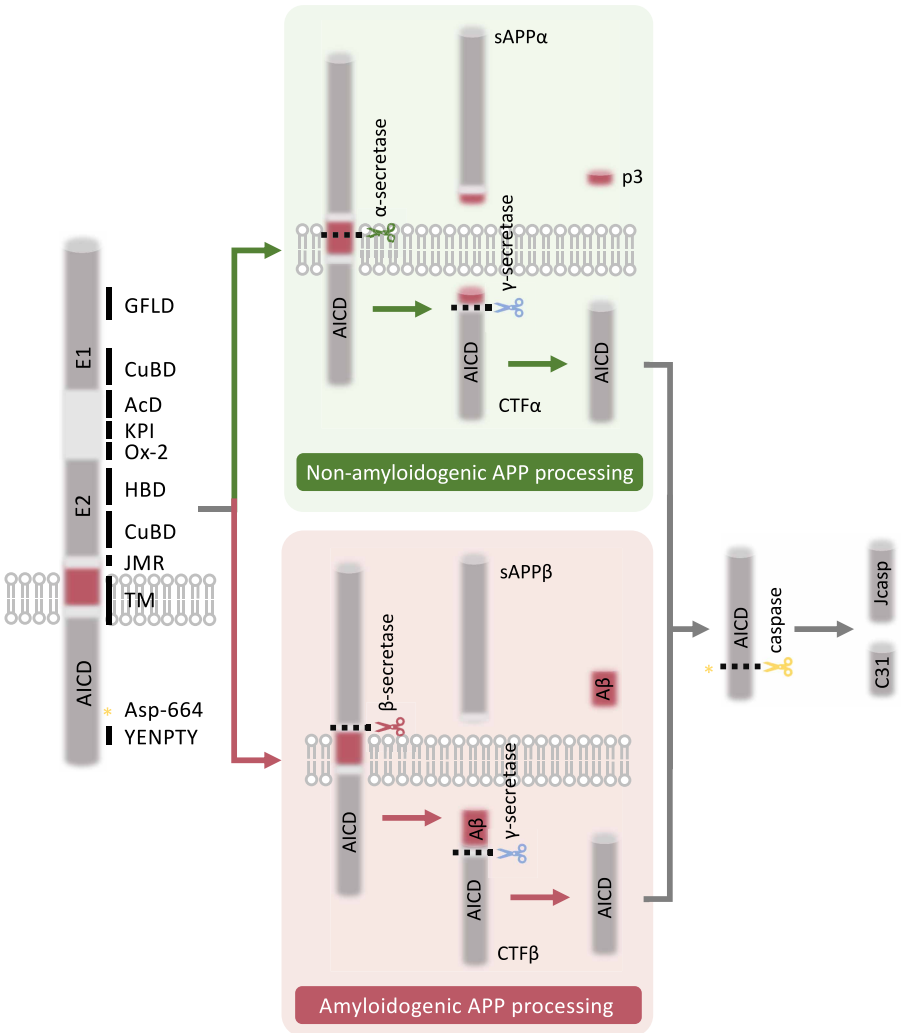

Figure 1. Schematic representation of APP structure and processing.

The ectoplasmic domain of APP constitutes E1 and E2 domains, which are connected by a AcD. The JMR connects the ectodomain to the center TM. E1 domain consists of a GFLD and a CuBD while E2 domain contains a HBD and a CuBD. Ox-2 and KPI domain are also present in the ectodomain of APP isoforms. In the cysolic domain, AICD possesses the YENPTY motif. Regulated intramembrane proteolysis of APP occurs in two distinct cleavage pathways, non-amyloidogenic and amyloidogenic processing. In non-amyloidogenic pathway, APP is cleaved within the Aβ-domain by α-secretase, releasing sAPPα and membrane-bound CTFα. Cleavage of CTFα by γ-secretase further secrets p3 fragment and AICD. In amyloidogenic pathway, APP is first cleaved by β-secretase, which releases sAPPβ and CTFβ. CTFβ is further processed by γ-secretase to release AICD and neurotoxic Aβ. AICD can be further cleaved by caspases at Asp-664, releasing two cytotoxic peptides, C31 and Jcasp. AcD, acidic domain; AICD, amyloid precursor protein intracellular domain; APP, amyloid precursor protein; Aβ, amyloid-β; CTFα, C-terminal fragment α; CTFβ, C-terminal fragment β; CuBD, copper-binding domain; E1, E1 domain; E2, E2 domain; GFLD, growth-factor-like domain; HBD, heparin-binding domain; JMR, juxtamembrane region; KPI, kunitz protease inhibitor domain; Ox-2, Ox-2 antigen domain; p3, p3 fragment; sAPPα, secreted APPα; sAPPβ, secreted APPβ; TM, transmembrane helix; YENPTY, tyrosine–glutamate–asparagine–proline–threonine–tyrosine domain.

regions. Indeed, AICD is reported to form a transcriptional regulatory complex with FE65 and the transcriptional coregulator Tat interactive protein 60 kDa (Tip60), which facilitates AICD-mediated transactivation signaling [42,43]. Moreover, AICD has been found to regulate various gene expression and thereby mediate different cellular processes (Table 2). In particular, AICD controls the expression of neuronal PAS domain Protein 4 (NPAS4), which incidentally controls the release of synaptic gamma-aminobutyric acid (GABA) [44].

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https://doi.org/10.1042/BST20241510

Table 1. List of AIPs which affect Aβ production

AIPs	Aβ production ↑ ↓	Proposed mechanism	References
Caveolin-3	↑	Up-regulate β-secretase-dependent APP cleavage through inactivating G-protein	[26]
FE65	↑	Regulate APP trafficking	[27–29]
GULP1	↑	Reduce APP expression on the cell surface	[30,31]
JIP1	↓	Transport and retain phospho-APP at neurite	[32,33]
LRP	↑	Elevate APP internalization	[34]
Dab1	↑	Increase surface APP expression	[35]
X11	↓	Translocate APP out of detergent-resistant Membrane (DRM) to suppress amyloidogenic processing	[21,36]
Numb	↑	Regulate the sorting of APP into recycling vesicles and decrease the level of cell surface APP	[37]
sorLA/ LR11	↓	Reduce surface APP expression by retaining APP in Golgi apparatus and attenuate BACE-dependent APP cleavage	[38]
CHF5074	↓	Reduces the interaction between APP and PS1, lowering γ-cleavage	[39]
		Binds to AICD and reduces its translocation to nucleus	[40]

AICD also regulates GluN2B expression, which affects synaptic *N*-methyl-D-aspartate receptor heterodimer assembly and, as a result, regulates excitatory neurotransmission [45].

Functions in neural networks

AICD is also implicated in differential functions in neurons. AICD is required during axonal transport. In transgenic Drosophila, overexpression of APP, but not the APP mutant lacking AICD, leads to defects in

Table 2. List of AICD-regulated genes in the nervous system

Gene	Gene expression ↑ ↓	Physiological function	References
APP	↑	Neurodevelopment	[46]
α2-actin	↑	Actin dynamics	[47]
BACE	↑	APP processing	[46]
CHOP	↑	Apoptosis	[48]
Cyclins B1 and D1	↑	Cell cycle activation	[49]
GluN2B	↑	Regulates neurotransmission	[45]
GSK3β	↑	Apoptosis, tau phosphorylation	[46]
KAI1	↑	Control cell motility and adhesion, apoptosis	[46]
NPAS4	↑	Regulate GABA release	[44]
Ptch1	↑	Regulate the proliferation of NPCs	[50]
p53	↑	Apoptosis	[51]
Tip60	↑	Histone acetyltransferase	[46]
Transgelin	↑	Actin dynamics	[47]
Tropomyosin	↑	Actin dynamics	[47]
VGLUT2	↑	Regulate vesicular uptake of glutamate and synaptic transmission	[52]

axonal transport. AICD mediates the interaction between APP and kinesin-I by directly binding to the kinesin-1 light chain. Furthermore, the axonal transport of APP to neuromuscular junctions (NMJs) is dependent on the interaction between AICD and kinesin-1 [53]. Additionally, the physiological roles of AICD in modulating the central nervous system (CNS) have been investigated *in vivo* in transgenic mouse models FeCγ12 and FeCγ25, both overexpressing AICD and FE65. Abnormal spiking events associated with enhanced seizure susceptibility are observed in these models when compared with mice overexpressing FE65 only [54]. Therefore, it is suggested that overexpression of AICD disrupts the neuronal circuit [54]. Furthermore, these models also demonstrate significantly increased activity of the kinase glycogen synthase kinase-3β (GSK-3β) [24]. The up-regulated activity of GSK-3β is associated with an increase phosphorylation of its downstream substrates which include collapsin responsive mediator protein–2 (CRMP2) protein, a key component of axonal guidance [24], and tau, which bind and stablise microtubule [24,55]. Aberrant phosphorylation of CRMP2 and tau disrupts their binding to microtubule [56,57]. Furthermore, AICD exerts its roles in cytoskeleton organization and dynamics by inducing the expression of genes encoding various regulators of actin dynamics, including transgelin and α2-actin [47]. While down-regulation of α2-actin in neural stem cells (NSCs) impairs NSC migration [58], transgelin knockout mice show cognitive impairments with spatial learning and memory deficits [59]. The above findings implicate proper expression of AICD is essential for the normal functions of neural networks.

Endoplasmic reticulum-mitochondrial signaling

AICD plays a role in maintaining endoplasmic reticulum (ER) calcium storage and mitochondrial functions. Cells lacking AICD (H4-AICD-VSV (Dox)) has shown to reduce ER calcium storage, which increases cytosolic calcium level, and subsequently reduces ATP production level and causes hyperpolarization of the inner mitochondrial membrane potential, indicating the physiological role of AICD in maintaining ER and mitochondrial functions [60]. AICD is shown to regulate the expression and transcription of phosphatase and Phosphatase and tensin homolog–induced kinase 1 (Pink-1) that modulates the turnover of mitochondria via mitophagy and control mitochondrial dynamics by reducing the level of dynamin-like protein 1 and mitofusin 2 [61]. Moreover, AICD also regulates the transcription of coiled-coil-helix-coiled-coil-helix domain containing 6 (CHCHD6), a core component of the multi-subunit protein complex which maintains mitochondrial homeostasis and cristae morphology [62].

AICD and its interactors in neurodevelopment

The aforementioned findings reveal the physiological significance of AICD. As stated above, AICD interacts with different proteins. Therefore, it is possible that some of the functions of AICD are contributed by recruiting different interactors. In the following, we will summarize the roles of AICD and its interactors in both neurodevelopment and neurodegeneration.

Neurogenesis

During neurogenesis, fully differentiated neurons and glia are generated from neural precursor cells (NPCs) in the embryonic brain. In the adult brain, neurogenesis persists in specific regions, like the hippocampus and the subventricular zone. Multiple lines of evidence suggest the role of AICD in neurogenesis, including regulation of NPCs proliferation and transcription. APP has been recognized as a negative modulator of neurogenesis as NPCs of $App^{-/-}$ knockout mice show significant elevated neurogenesis [63]. The effect of APP on neurogenesis has been shown to be associated with AICD. In an AD mouse model carrying the Swedish and Indiana familial AD mutations, platelet-derived growth factor B-chain promoter-driven APP transgenic mice (PDAPP), a mutation that prevents caspase cleavage of AICD to produce C31 peptide leads to a reduction in hippocampal neuronal precursor proliferation when compared with PDAPP mice without the mutation [64]. Furthermore, inhibited caspase cleavage of AICD may also interfere with the intermolecular interactions that involve AICD. For adult neurogenesis, transgenic mouse models FeCγ12 co-expressing AICD and FE65 demonstrates reduction in proliferation adult hippocampal progenitor cells (HPC). However, such reduction in HPC proliferation is not observed in Fe27 transgenic models which overexpress solely FE65. This implicates the role of AICD in suppressing adult neurogenesis in HPC [65]. Additionally, overexpression of AICD can reverse the aberrant neurogenesis in transient axonal glycoprotein (TAG1) knockout mice. Conversely, AICD with a mutated FE65-binding YENPTY motif cannot reverse such effect of TAG1 knockout on neurogenesis, suggesting that both AICD and FE65 participate in neurogenesis [63].

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https://doi.org/10.1042/BST20241510

As mentioned earlier, AICD is reported to form a transcriptional regulatory complex with FE65 and Tip60 [42,43]. During neurogenesis, this tripartite complex regulates genes that are implicated in neurogenesis, including stathmin [66]. Stathmin is a neuronal protein that is associated with adult neurogenesis [67]. During embryonic development, AICD acts as a negative regulator of Wnt signaling, which mediates NPCs proliferation and differentiation, through its interaction with GSK3β, a regulator of Wnt signaling activation [68]. The AICD/GSK3β interaction stimulates the kinase activity GSK3β, resulting in an inhibitory effect on Wnt signaling and NPCs proliferation. Moreover, AICD facilitates the functions of nerve growth factor (NGF) in inducing the expression of cyclin-dependent kinase (CDK) inhibitors, including that of p15, p16 and p21, thereby, suppressing NPCs proliferation [68].

Neuronal migration and positioning

The organization of neurons into differential layers of the cerebral cortex during neuronal migration and positioning is essential for the establishment of the CNS. In the embryonic brain, the absence of APP leads to migration defect of NPCs into the cortical plate [69]. AICD interactor Dab1 is an adaptor protein implicated in neuronal migration in the developing cerebral cortex[70,71]. The interaction between full-length APP and Dab1 through AICD is crucial as a mutation in the AICD YENPTY motif and knockdown of Dab1 diminishes the stimulatory effect of APP on neuronal migration into the cortical plate [15,69]. Further elucidation reveals the involvement of disrupted-in-schizophrenia 1 (DISC1) in APP-Dab1 pathway in neuronal migration. Knockdown of APP disrupts the subcellular localization of DISC1 at the centrosome, which is required for proper cortical cell migration into the cortical plate [72]. Furthermore, the overexpression of DISC1 successfully rescues the migration defects caused by the knockdown of APP and Dab1, respectively, but not vice versa [72]. The effect of DISC1 on APP/Dab1 pathway maybe contributed by its interaction with APP-Dab1 complex [72].

The role of APP during neuronal positioning has been suggested by $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$triple knockout mice which exhibit cortical dysplasias, a characteristic of defective neuronal positioning [73]. The function of APP in this process is likely contributed, at least in part, by its interaction with FE65 through its AICD as such neuronal defects resemble those observed in $FE65^{-/-}$/FE65 Like 1 $(FE65L1)^{-/-}$ double knockout mice [74]. Expression of APP and FE65 significantly up-regulates cell movement mediated by APP, suggesting the role of APP-FE65 complex in cell motility [75]. In fact, APP and FE65 may recruit regulators of the cytoskeleton, like β1-integrin and mammalian homolog of Drosophila Enabled (Mena) [75]. Moreover, the APP/FE65 complex colocalises with Mena in β1-integrins at focal complexes in mobile membrane compartments, implicating the role of the interaction between full-length APP and FE65 through AICD in processes related to integrin-based adhesion and migration [75].

Neurite outgrowth and axonal guidance

During the establishment of the neuronal circuitry, neurite outgrowth generates projections from newly differentiated neurons to form axons and dendrites. Axonal guidance then ensures that axons of newly differentiated neurons are extended to reach their synaptic targets under the effect of guidance cues. AICD is a promoter of neurite outgrowth by acting as a Wnt antagonist [68]. AICD enhances the effect of NGF-dependent induction of neurite outgrowth by attenuating Wnt3a signaling which suppresses the effect of NGF physiologically [68]. The role of APP family proteins in axonal guidance has been revealed as defects in midline crossing of projection axons in $App^{-/-}/Aplp2^{-/-}$ double-knockout mice has been observed [76]. Moreover, binding of Slit2, a glycoprotein that implicates in axonal guidance, to the E1 domain of APP has been shown to mediate APP/FE65/p21-activated kinase 1 (PAK1) multimeric complex formation, and resulted in enhanced axon projection [76]. As PAK1 is a regulator of actin dynamics, the above finding further supports the role of APP/AICD and FE65 in axonal guidance. However, further investigations are required to elucidate the mechanism by which this multiprotein complex activates PAK1. Of note, FE65 concurrently interacts with ADP-ribosylation factor 6 (ARF6) and the Rac1- guanine nucleotide exchange factor complex, Engulfment and Cell Motility 1/dedicator of cytokinesis 1 to stimulate Rac1 [77,78]. Further investigations are still underway to determine the exact implications of these complexes in cytoskeleton remodeling.

Synaptogenesis

The assembly of synapses between neighboring nerves or between muscles facilitates the rapid transmission of signals. $App^{-/-}/Aplp2^{-/-}$ double-knockout mice develop aberrant nerve terminal sprouting with a reduction of synaptic vesicles at the presynaptic terminals, implicating their roles in synaptogenesis [79]. AICD is

indispensable for the generation of synaptic connections. The phenotype comprising of synaptic loss observed in the PDAPP AD mouse model could be rescued by an APP mutation that abolishes the generation of C31 from AICD by caspase cleavage at Asp-664 (Figure 1) [64]. It is suggested that AICD is essential for maintaining normal synaptic functions which are impaired in AD [64]. The effect of AICD for inducing axonal arborization is suggested to be mediated by its interaction with Dab1, an adaptor protein for Abl tyrosine kinase, a key regulator of synaptic plasticity, which also interacts with full-length APP through AICD [80,81]. Additionally, $App^{-/-}/Aplp2^{-/-}$ double-knockout mice exhibit multiple NMJ defects, including aberrant nerve terminal sprouting, diffused synaptic distribution and abnormal apposition of presynaptic vesicle proteins and postsynaptic acetylcholine receptors, suggesting the regulatory roles of APP and APLP2 during NMJ development [79,82]. The role of AICD during NMJ formation is further demonstrated in $Aplp2^{-/-}$ knockout expressing secreted sAPPα, whereby sAPPα is insufficient to compensate for the NMJ deficits observed in models deficient of APLP2 [83]. Noteworthy, the interaction between AICD and FE65 may be relevant to the physiological role of APP on neuromuscular synaptogenesis, as similar NMJ defects are also seen in a mouse expressing an APP mutant, that lack the last 15-amino acid of APP, on an $Aplp2^{-/-}$ background [84]. The FE65 interacting YENPTY motif is located within the deleted region. Moreover, compound knockout of APLP2 with either FE65 or FE65L1 intensifies the severity of NMJ impairments [85]. The above findings support the role of AICD-FE65 in NMJ formation.

Additionally, the interaction between *Drosophila* homologue APP-like (APPL) and *Drosophila* X11 (dX11) through AICD is crucial for synaptogenesis as the presynaptic expression of mutant APPL or dX11 lacking the critical YENPTY sequence and PTB domain significantly attenuated synaptic formation [86]. It has been reported that APP forms a macromolecular protein complex that induces presynaptic differentiation and the formation of the presynaptic active zone by coupling with X11 and calcium/calmodulin-dependent serine protein kinase (Cask) through the YENPTY motif of APP [87].

AICD and its interactors in neurodegeneration

Neurodegeneration refers to the progressive loss of neurons in the CNS. As neurons are generally post-mitotic, the loss of neurons often implicates the irreversible development of neurodegenerative diseases, such as AD. There are several biochemical pathways that contribute to neuronal death, including the disrupted ER-mitochondria signaling [88], accumulation of neurotoxic peptides [89,90] and the propagation of excitotoxicity [91,92]. These biochemical pathways often lead to the initiation of an apoptotic cascade and eventually cause progressive neuronal death. Since the proposal of ACH, APP and Aβ have become the centers of AD research. As an inevitable product of APP processing, AICD also exerts an important role in neurodegeneration. AICD levels in AD patients are significantly higher than that in non-demented controls [55]. Specifically, AICD has been shown to modulate neuron-specific apoptosis [55,93,94]. Overexpression of AICD in transgenic mice displays AD-like abnormalities, including tau hyperphosphorylation and intracellular aggregation of neurofibrillary tangles, as the activity of GSK-3β, which contributes to hyperphosphorylation of tau, has been elevated [24,55]. Overexpression of AICD also increases the age-dependent loss of hippocampal neurons by inducing neuronal susceptibility to excitotoxic stimuli [55]. Amyloidogenic processing of APP is more pronounced in AD, resulting in increased production of amyloidogenic APP cleavage fragments. Since the overexpression of APP and its cleavage products is implicated in various processes that lead to neurodegeneration, this highlights the importance of the overall role of APP and its cleavage products, including AICD, in neurodegenerative diseases.

Neuronal apoptosis

AICD controls apoptotic pathways by modulating expressions of various proteins through transcriptional regulations. For example, AICD interacts with p53 mRNA and promotes the expression of p53 and its shorter isoform p44, resulting in the activation of p53/p44-mediated proapoptotic signaling pathways. This results in an enhancement of caspase activity [95] and tau hyperphosphorylation in neurons [96]. Recent studies demonstrate that AICD induces ER-stress by enhancing nuclear retention of FoxO3a, a transcription factor involved in neuronal ageing and cell death [97]. During ER-stress-induced apoptosis, AICD also up-regulates C/EBP homologous protein (CHOP) expression by binding to the CHOP promotor and potentiates ER-stress-induced apoptosis [48,98]. Similarly, it also regulates mitochondria homeostasis by up-regulating the transcription of *PINK1*, which encodes Pink-1, a mitochondrial kinase [61]. Since AICD does not consist of a nuclear localization sequence, it is suggested that AICD translocates into the nucleus to exert the above transactivation

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functions by forming the AICD-FE65-Tip60 complex [48,95,98,99]. AICD-FE65 also complexes with the transcription factor CP2/LSF/LBP1 [90,100]. This complex induces the transcription and expression of human GSK3β [90,101]. It is found that the knock down of neuronal GSK3β can reverse capspase 3 activation-induced cell death, indicating GSK3β activation can induce neuronal cell death by promoting caspase 3 activation [102].

Besides acting as a transcription factor for proapoptotic proteins, AICD has been found to participate in inducing apoptosis via regulating protein-protein interaction. For example, it is proposed that the phosphorylation of AICD Thr668 weakens AICD-FE65 interaction which releases FE65 for the binding with Bloom syndrome protein (BLM) in the nucleus. Such FE65-BLM complex in nucleus facilitates the re-initiation of DNA replication [103], a process known to associate with apoptosis [104,105]. Furthermore, FE65 can interact with teashirt3 to suppress AICD-FE65 mediated transcriptional activity, yet enhance the inhibition of caspase 4 expression in a FE65-teashirt3 complex-mediated manner [106]. As caspase 4 contributes to both ER-stress-induced apoptosis [107] and innate inflammation response [108], it is suspected that FE65 may participate in neuronal apoptosis by regulating the expression and activity of caspase 4. PTB-containing JIP1 is another AICD interactor predominantly expressed in neural tissues [32]. However, unlike FE65, plenty of JIP1-mediated pathways have been reported to be dependent on the JNK activation pathway. Under UV stress, Aβ exposure and hypoxia, the decrease in JIP1 expression causes neurons to be more prone to JNK-mediated apoptosis [109]. In addition, in response to cytokine, JIP1 is shown to co-operate with Islet-brain 1 (IB1) to modulate apoptosis as an elevated expression of JIP1 and IB1 protects cells from apoptosis [110]. Altogether, JIP1 has an anti-apoptotic potential that can be considered as a neuroprotective factor. Interestingly, JIP1 mediates the phosphorylation of APP and AICD at Thr668 via JNK kinase activity [111]. The phosphorylation of AICD Thr668 increases AICD-induced apoptosis and increases Aβ production [112,113], suggesting that JIP1 promotes apoptosis by facilitating AICD phosphorylation.

Neuroinflammation and neurodegeneration

In addition to intracellular pro-apoptotic signaling pathways, progressive neuronal loss can also be caused by aberrant neuroinflammation. Neuroinflammation is generally considered a neuroprotective mechanism, as it helps eliminate pathogens in the CNS and facilitates the repair of neurons from extracellular insults. However, chronic neuroinflammation has emerged as a major risk factor for age-related neurodegenerative disorders, including AD and Parkinson's disease [114,115]. In AD, the expression levels of pro-inflammatory cytokines, such as interleukins-1 (IL-1), IL-6, IL-8, and tumor necrosis factor α (TNFα), are significantly up-regulated, indicating an inflamed brain environment [116,117]. Activated microglia, the primary macrophages in the CNS, are responsible for releasing these cytokines as the primary source of local inflammatory response in the AD brain [116,118]. Emerging evidence has indicated that APP processing and the AICD may play a role in neuroinflammation as APP is expressed and can be processed in microglia and astrocytes [119]. Inhibiting APP processing in macrophages has been shown to suppress their immunological activities [120]. Similarly, the expression of AICD in transgenic mice has been found to positively induce neuroinflammation [65]. Moreover, the anti-neuroinflammatory drug 1-(3′,4′-dichloro-2-fluoro[1,1′-biphenyl]-4-yl) cyclopropanecarboxylic acid (CHF5074) can effectively decrease neuroinflammation by limiting the expression of pro-inflammatory elements [121]. Interestingly, CHF5074 can interact with AICD fragment and decrease its transcriptional activity and transcriptional output of AICD-regulated genes, like *KAI1*, by reducing nuclear translocation of AICD [40,122]. These further suggest the potential role of AICD in neuroinflammation. In the cerebrospinal fluid samples of AD patients, several AICD associating proteins, including fibrinogens and peroxiredoxin, which are important for neuroinflammation, have been found to be increased in expression [123–125]. Although the precise mechanisms by which AICD can affect neuroinflammation remain to be elucidated, these findings raise the intriguing speculation that AICD may regulate microglia activation and the expression of pro-inflammatory proteins.

As mentioned, AIPs have been shown to promote amyloidogenic processing of APP to increase Aβ as well as AICD generation (Table 1). Therefore, these interactors participate in neuroinflammation by triggering the production of AICD. Additionally, AICD-AIP complex may contribute neuroinflammation by alternative mechanism as some of these AIPs have been shown to participate in neuroinflammation. For example, GULP1 contributes to the ATP-binding cassette transporter A1 (ABCA1) pathway and regulates astrocytic phagocytosis during ischemic injury [126]. FE65-teashirt3 complex also regulating caspase 4 expression [106], in which caspase 4 is required for the activation of inflammasomes via activating caspase 1 [127]. Nevertheless, the above findings implicate the association of AICD and its interactors in neuroinflammation.

Dysregulation of ER-Mitochondrial signaling

Increase in oxidative stress and mitochondrial dysfunction are recognized as the early events in the progression of sporadic AD [128,129]. In recent years, the proposal of the mitochondrial cascade hypothesis (MCH) believes that mitochondrial dysfunction is the primary cause of AD, as mitochondrial dysfunction causes energetic and/or metabolic impairment and directly leads to neuronal loss. Therapeutic approaches to restoring mitochondrial function have also been shown to effectively slow down the progression of the disease. For example, physical exercise can enhance mitochondrial function and serve a neuroprotective role against AD [130]. A plant-based antioxidant, resveratrol, also shows neuroprotective effects as it protects mitochondria by decreasing mitochondrial oxidative stress and increasing mitochondrial biogenesis [131]. In the APP/PS mice model, the administration and delivery of resveratrol to the brain can significantly improve memory function [132]. Despite MCH suggesting APP processing and amyloid production are the results of mitochondrial dysfunction, in fact, AICD, as the product of APP processing, can in turn cause mitochondrial dysfunction.

As mentioned, the nuclear signaling of AICD is often associated with FE65-mediated nuclear translocation. AICD-FE65 is responsible to act on increasing the expression of α2-actin and transgelin that destabilize actin fibers in neurons [47]. Since mitochondrial function is highly sensitive to actin dynamics, it is reported that AICD-FE65-mediated actin dynamic leads to a significant decrease in mitochondrial membrane potential and ATP production [133]. FE65 also interacts with Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase 2 (SERCA2). As SERCA2 is an important protein for cellular calcium homeostasis, it is reported that FE65-SERCA2 interaction plays an important role in determining cell viability under ER stress by affecting intracellular calcium homeostasis [134]. Notably, it is also reported that the level of cytosolic calcium was elevated in presenilin double knockout mice, suggesting a disrupted SERCA activity [135]. As presenilin is essential for APP γ-cleavage, it is suggested that the absence of AICD can disrupt SERCA-dependent calcium signaling [136]. It is proposed that the interaction of AICD and FE65 may further complex with SERCA2 to regulate ER calcium homeostasis [134]. Numb depletion increases Rho-associated coiled-coil containing protein kinase 1 (ROCK1) activation that enhances dynamin-related protein 1 translocation to mitochondria, consequently promoting mitochondria fragmentation [137]. Intriguingly, ROCK1 is able to interact with and phosphorylate APP at Ser655 to up-regulate amyloidogenic processing [138], which suggests a role of Numb in regulating mitochondrial homeostasis via ROCK-1 induced APP processing.

Additionally, increasing findings suggest that the disruption of ER-mitochondria signaling in AD [139–141]. The communication between ER and mitochondria is essential in regulating numerous cellular events, including calcium and lipid metabolism and UPR response [142–144]. In post-mortem AD brains, the protein expressions of vesicle-associated membrane protein-associated protein B (VAPB) and protein tyrosine phosphatase interacting protein-51 (PTPIP51) are found to be decreased in cortex, indicating the disruption of ER-mitochondria contact in AD brain [139]. Using cell model of AD, the localization of CTFβ increases in mitochondrial-associated ER membranes (MAM), resulting in altering the lipid composition of MAM, ultimately causing mitochondrial dysfunction [145]. Another study also demonstrated the accumulation of CTFβ in ER induces the uptake of cholesterol and cholesterol trafficking from plasma membrane to MAM, reveal a new role of CTFβ in cholesterol disturbances in AD [140]. γ-Secretase activating protein (GSAP) plays a crucial role in regulating γ-secretase activity and has recently been found to participate in mitochondrial function by forming a GSAP-FE65-APP ternary complex. It is proposed that FE65, GSAP and APP-CTR colocalize in MAM. In AD condition, FE65 recruits GSAP to dephosphorylate APP, inducing Aβ production in MAM, which impairs the lipid homeostasis of ER and mitochondria [146].

Future perspectives

The APP interactome play essential physiological roles during the establishment and maintenance of the neuronal system [147]. In the present review, we have highlighted the indispensable role of AICD in regulating neuronal function, and its contribution to neurodevelopment and neurodegeneration through the interaction between AICD and its binding partners (Figure 2). Over the past decades, the identification of AICD binding partners has aided in understanding the complexity of the roles of AICD in various cellular pathways and has provided us hints of how important APP processing is for neuronal functions from early age, during neurodevelopment, to adulthood neuronal maintenance. Therefore, a comprehensive illustration of the AICD interactome helps to decipher the pathophysiology of AD and suggest druggable targets.

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https://doi.org/10.1042/BST20241510

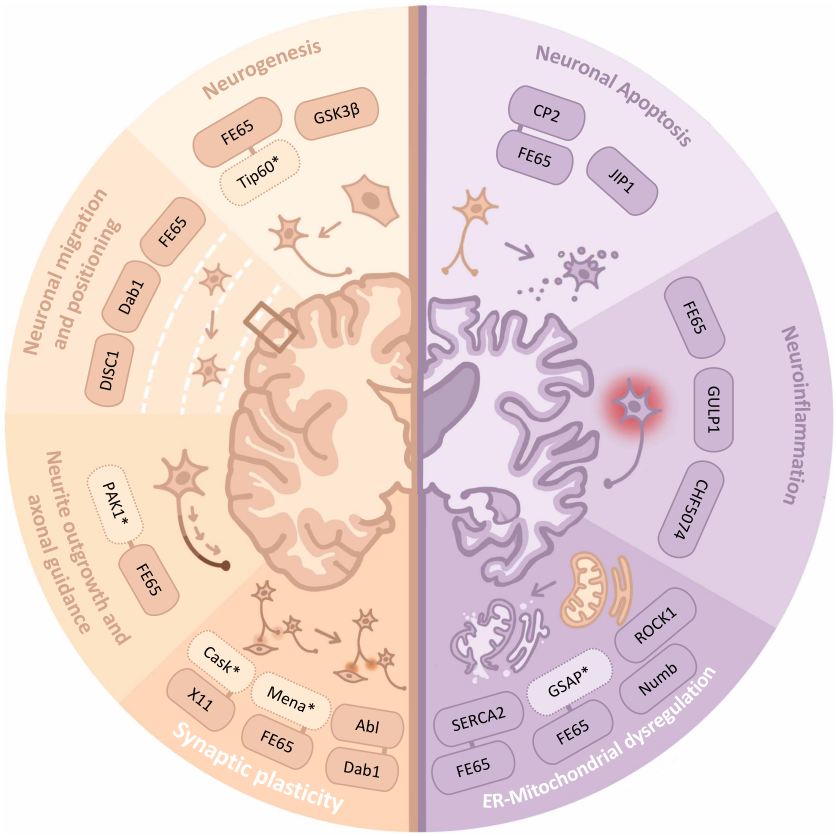

Figure 2. Summary of AICD interactors implicated in neurodevelopment and neurodegeneration.
AICD interactors that are associated with different stages of neurodevelopment (orange) and neurodegeneration (purple) are illustrated. TAG1, transient axonal glycoprotein; Tip60, Tat interactive protein 60 kDa; Dab1, Disabled-1; DISC1, disrupted-in-schizophrenia 1; PAK1, p21-activated kinase 1; Cask, calcium/calmodulin-dependent serine protein kinase; Abl, Abl tyrosine kinase; JIP1, JNK-interacting protein 1; CHF5074, 1-(30,40-dichloro-2-fluoro[1,10-biphenyl]-4-yl) cyclopropanecarboxylic acid; GULP1, GULP PTB domain containing engulfment adaptor 1; SERCA2, Sarcoplasmic/ Endoplasmic Reticulum Calcium ATPase 2.

The functional redundancy of APP family proteins during neurodevelopment is demonstrated by single-, double- and triple-knockout mouse mutants. While single-knockout of APPs only leads to subtle phenotypes in mice, double- and triple-knockout of APPs show lethal early postnatally [73,148,149]. The functional compensation between APPs could be due to the overlapping interactome which may stimulate similar signaling pathways. Although ALPL1 and APLP2 lack the Aβ domain, the APPs share a high degree of structural homology and similar presenilin-dependent RIP proteolytic processing as substrates of γ-secretase, which releases the intracellular domains (ICDs) of sizes ∼6 kDa [150]. AICD, APLP1 and APLP2 ICDs (AL1ICD and AL2ICD) are highly similar and possess a conserved structure consisting of motifs, including the caspase cleavage site and YENPTY domain.

The protein-protein network of the AICD interactome co-ordinates cellular functions of AICD as signals received are relayed through the concerted and synchronized actions of functional components of the proteome. It is therefore important to investigate the contribution of the spatio-temporal dynamics of these interactions in the cellular signaling pathways when characterizing the AICD interactome. For example, AICD, AL1ICD and AL2ICD possess differences in cellular localization and nuclear signaling capabilities. While both AICD and AL2ICD bind to FE65 and translocate into the nucleus where they form nuclear AFT complexes, FE65 interacts with the APLP1 holoprotein, resulting in retention of FE65 and AL1ICD in in the extranuclear regions and decreased nuclear AFT complex formation [151]. In addition, full-length APLP1 exhibits slower turnover than APP and APLP2, which may account for a lower availability of AL1ICD and thus reduced ARF

complex formation [151]. The differences in the compartmentalization and affinity between ICDs of APPs and their interactors can result in differential levels of downstream signaling. Comparative investigations of the interactions between AICD, AL1ICD and AL2ICD and their shared binding partners using cryo-electron tomography can enable *in situ* structural studies in unperturbed cellular environments at 3–4 nm resolution, visualizing the localization of macromolecules in cells [152].

The interactions between AICD and its binding partners are dependent on their states of phosphorylation. On AICD, differential phosphorylation statuses of Tyr682 and Thr668 influence the composition of the APP interactome [153–155]. In AD brains, there is an increase in phosphorylation of Tyr682 and Thr668 residues on AICD [156,157], suggesting the implications of phosphorylation and the altered AICD interactome in AD pathogenesis. Furthermore, phosphorylation statuses of AICD, AL1ICD and AL2ICD have varying effects in shaping the ICDs interactome. Phosphorylation of AICD interactors also contributes regulatory mechanisms of signaling pathways involving AICD. For example, the phosphorylation status of FE65 at Ser288 and Ser610 modulate FE65-APP transcriptional activity and APP processing mediated by FE65, respectively [158,159]. Nevertheless, the dynamics of the interactome network created by phosphorylation and dephosphorylation of specific residues of AICD and its interactors as well as the precise effects of these interactions are yet to be further elucidated.

Overlapping features are observed in both neurodevelopmental and neurodegenerative disorders. For instance, AICD, as we have summarized, possesses dual roles in both neurodevelopment and degeneration. Similarly, GSK3 signaling is associated with both neurodevelopmental and degenerative function. GSK3 cycles between on/off states through phosphorylation at different sites whereas Ser9 and Ser21 are considered inactive sites and Tyr216 is considered an active site. LiCl is an FDA-approved drug that manipulates this molecular switch to inactivate GSK3 and to reduce tauopathy and Aβ production [160,161]. Aforementioned, AICD changes its localization and participates in different cellular pathways via interacting with different binding partners. Therefore, manipulating AICD interacting dynamic using small-molecule compounds and peptides have become new therapeutic strategies to treat AD. For example, CHF5074 is an anti-inflammatory compound that targets AICD and reduces its nuclear translocation and transcriptional activity through its interaction with AICD [40]. However, it is to be further investigated whether the neuroprotective abilities of CHF5074 in lowering brain plaque burden and reducing neuroinflammation could be explained by its targeting against AICD activities [122]. Peptide targeting APP-X11 interaction at AICD has also been reported to successfully reduces Aβ levels in neurons by attenuating the interaction [162]. FE65 is known to up-regulate amyloidogenic APP processing through its interaction with AICD. The blockage of FE65-AICD interaction is therefore considered as a promising strategy to decrease Aβ secretion. For example, pentapeptide P33, which interacts with the N-terminal WW domain of FE65, decreases Aβ production and improves learning ability and memory functions in AD animal model by inhibiting FE65-AICD interaction [163]. Additionally, X11 proteins interacts with AICD and in turns inhibits amyloidogenic processing. Brandimarti et al. [164] has introduced gPTB9TM chimeric protein, which is comprised by a N-terminal GFP protein, followed by the PTB domain of X11 protein and transmembrane domain of US9 at the C-terminus. The transmembrane domain of this chimeric protein allows it to localize closely to APP and anchors the PTB domain adjacent to AICD. The expression of gPTB9TM drives the interaction of AICD and the X11-derived PTB domain, resulting in the decrease in amyloidogenic processing [164]. Despite plenty of AICD-targeted therapies aim on attenuating amyloidogenic APP processing, it is worth noting that AICD also holds the positive roles in promoting neurogenesis. With the emerging trend of neuro-regeneration therapies, it is possible that AICD can be a new target to trigger neuro-regeneration.

Perspectives

- Research into AICD and its interactome extends our understanding of their roles in both neurodevelopment and neurodegeneration.
- AICD interacts with different interactors to form functional complexes to regulate wide range of processes within the nervous system.
- The manipulation of the interaction between AICD and its interactors can be the drug target for tackling and ameliorating neurodegenerative pathology.

Biochemical Society Transactions (2024) **52** 2539–2556
https://doi.org/10.1042/BST20241510

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Funding

This work was supported by funds from the Research Grants Council Hong Kong, Health and Medical Research Fund (Hong Kong), CUHK direct grant scheme, United College endowment fund and the TUYF Charitable Trust.

Author Contribution

L.L.H.N., J.C. and K.F.L. wrote the manuscript.

Abbreviations

APP, amyloid precursor protein; ABCA1, ATP-binding cassette transporter A1; AcD, acidic domain; ACH, amyloid cascade hypothesis; AD, Alzheimer's disease; AICD, APP intracellular domain; AIP, AICD interacting proteins; AL1ICD, APLP1 ICDs; AL2ICD, APLP2 ICDs; APLP, APP-like protein; APPL, APP-like; APPswe, APP Swedish mutation; ARF6, ADP-ribosylation factor 6; Aβ, amyloid-β; BACE, beta-secretase 1; BLM, Bloom syndrome protein; Cask, calcium/calmodulin-dependent serine protein kinase; CDK, cyclin-dependent kinase; CHCHD6, coiled-coil-helix-coiled-coil-helix domain containing 6; CHF5074, 1-(3′,4′-dichloro-2-fluoro [1,1′-biphenyl]-4-yl) cyclopropanecarboxylicacid; CHOP, C/EBP homologous protein; CNS, central nervous system; CRD, cysteine-rich domain; CRMP2, collapsin responsive mediator protein–2; CTFα, C-terminal fragment α; CTFβ, C-terminal fragment β; CuBD, copper-binding domain; Dab1, Disabled-1; DISC1, disrupted-in-schizophrenia 1; dX11, *Drosophila* X11; ER, endoplasmic reticulum; FE65L1, FE65 Like 1; FoxO3a, Transcription factor forkhead box O3 protein; GABA, gamma-aminobutyric acid; GFLD, growth-factor-like domain; GSAP, γ-Secretase activating protein; GSK3β, glycogen synthase kinase-3β; GULP1, GULP PTB domain containing engulfment adaptor 1; HBD, heparin-binding domain; IB1, Islet-brain 1; IL, Interleukins; JIP1, JNK-interacting protein 1; JMR, Juxtamembrane region; KPI, Kunitz protease inhibitor; LRP, lipoprotein receptor protein family; MCH, mitochondrial cascade hypothesis; Mena, Mammalian enabled; NGF, nerve growth factor; NMJ, neuromuscular junction; NPAS4, neuronal PAS domain Protein 4; NPCs, neural precursor cells; Ox-2, Ox-2 antigen domain; PAK1, p21-activated kinase 1; PDAPP, promoter-driven APP transgenic mice; Pink-1, phosphatase and tensin homolog–induced kinase 1; PTB, phosphotyrosine-binding; Ptch1, Patched1; RIP, regulated intramembrane proteolysis; ROCK1, Rho-associated coiled-coil containing protein kinase 1; sAPPα, secreted APPα; sAPPβ, secreted APPβ; SERCA2, Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase 2; TAG1, transient axonal glycoprotein; Tip60, tat interactive protein 60kDa; TM, transmembrane helix; TNFα, tumor necrosis factor α; VGLUT2, vesicular glutamate transporter 2; YENPTY, tyrosine–glutamate–asparagine–proline–threonine–tyrosine.

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