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Cellular Trafficking of Amyloid Precursor Protein in Amyloidogenesis Physiological and Pathological Significance

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Abstract

The accumulation of excess intracellular or extracellular amyloid beta (Aβ) is one of the key pathological events in Alzheimer's disease (AD). Aβ is generated from the cleavage of amyloid precursor protein (APP) by beta secretase-1 (BACE1) and gamma secretase (γ-secretase) within the cells. The endocytic trafficking of APP facilitates amyloidogenesis while at the cell surface, APP is predominantly processed in a non-amyloidogenic manner. Several adaptor proteins bind to both APP and BACE1, regulating their trafficking and recycling along the secretory and endocytic pathways. The phosphorylation of APP at Thr668 and BACE1 at Ser498, also influence their trafficking. Neurotrophins and proneurotrophins also influence APP trafficking through their receptors. In this review, we describe the molecular trafficking pathways of APP and BACE1 that lead to Aβ generation, the involvement of different signaling molecules or adaptor proteins regulating APP and BACE1 subcellular localization. We have also discussed how neurotrophins could modulate amyloidogenesis through their receptors.

Keywords APP · BACE1 · Cellular trafficking · Gamma-secretase · Amyloidogenesis

Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60–80% of all cases [1], and is the sixth leading cause of death in the USA [2]. Currently, 47 million people worldwide are afflicted with AD. This number is expected to increase to 131 million people by the year 2050 [3]. The AD brain displays several cellular pathologies, such as extracellular amyloid plaques that contain aggregates of amyloid beta (Aβ), intraneuronal neurofibrillary tangles (NFTs), and cerebrovascular deposits of Aβ fibrils [4, 5]. Aβ is generated through the amyloidogenic processing of amyloid precursor protein (APP) by two distinct proteolytic enzymes within the cell: BACE1 and γ-secretase [6, 7]. APP can also be processed non-amyloidogenically through combined α- and γ-secretase actions [8]. The amyloidogenic processing of APP is determined by its subcellular localization and convergence with BACE1 and γ-secretase. Thus, understanding the intracellular trafficking of these three key molecules is essential to identify the molecular mechanism of Aβ generation. Moreover, we have recently found that $p75^{NTR}$, a neurotrophin receptor, enhances APP and BACE1 internalization and modulates APP amyloidogenic processing in a proneurotrophin-dependent manner [9]. In this review, we summarize the properties, signaling, and the trafficking of APP, BACE1, and γ-secretase, their interaction with other proteins, and the role of neurotrophins in amyloidogenesis.

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Generation of Aβ

Aβ exists as soluble or an insoluble form and aggregate to form dimers, oligomers, or fibrils [10]. The soluble Aβ secondary structure primarily consists of α-helices stabilized by the cell

membrane while insoluble Aβ consists mainly of β-sheets [11]. When soluble Aβ is released from the membrane, it converts its α-helices to β-sheets, forming the insoluble and toxic peptides [11]. The insoluble peptides are prone to aggregation and plaque formation. In humans, the accumulation of Aβ peptides might take 10–20 years before any clear clinical diagnosis [11].

Aβ is generated from APP. In the cell, APP is processed by two distinct pathways, the amyloidogenic and the non-amyloidogenic processing pathways. In the amyloidogenic pathway, APP is first cleaved by BACE1 which releases the soluble ectodomain region of APP (sAPPβ). The remaining C terminal fragment is a 99-amino acid fragment containing the precursor for Aβ, CTFβ (also referred to as C99) [8, 12]. CTFβ is then first cleaved at the ε cleavage site through γ-secretase endopeptidase activity, releasing the APP intracellular domain (AICD) and the Aβ fragment, which is 48- or 49-amino acids in length [12]. This is followed by γ-secretase carboxypeptidase activity at the ζ and γ cleavage sites, further processing the Aβ fragment for a final length of 40- and 42-amino acids (also referred to as $Aβ_{40}$ and $Aβ_{42}$, respectively) [12]. The non-amyloidogenic pathway occurs when APP is cleaved by α-secretase and γ-secretase, releasing the soluble ectodomain region cleaved at the α-secretase site (sAPPα). The ectodomain region contains a part of the truncated Aβ region, the remaining Aβ fragment (p3), and the CTFα region. It is composed of 83-amino acids (C83) [8, 13]. Enzymes that have α-secretase activities are members of the A disintegrin and metalloproteinase (ADAM) family: ADAM 9, ADAM 10, and ADAM 17 [14].

APP, a type-I integral membrane glycoprotein, is widely expressed in neuronal and non-neuronal cells and in various peripheral organs and tissues [8, 15]. APP has at least three isoforms categorized by the total number of amino acids: APP_{770} with 770-amino acids, APP_{751} with 751-amino acids, and APP_{695} with 695-amino acids [8]. APP_{770} contains a Kunitz protease inhibitor and Ox-2 antigen domain while APP_{751} has only Ox-2 [15]. APP_{695} do not have these two domains. Although all three isoforms are amyloidogenic, it is the APP_{695}, mainly expressed in neurons [8], that is preferentially processed to generate Aβ [16]. APP function is not limited to Aβ generation, but its critical role in AD has encouraged most researchers to focus on APP processing that leads to AD. The neuronal form APP_{695} is involved in the following functions: synaptogenesis, neurite outgrowth, and cell targeting during embryonic brain maturation [17], neuromuscular endplate formation and maintenance [18], maintaining the plasticity of dendritic spines in adult brain [19], synaptic plasticity and transmission, and learning and memory [20]. Pathologically, APP upregulation was also correlated with tumor progression, migration, and invasion of several types of cancers, such as germ cell, breast, prostate, pancreatic, and colon cancers [21].

BACE1 is ubiquitously expressed in the body but is highly expressed and more active in the brain [22, 23]. It is a type-I membrane protein that contains 501-amino acids with an N-terminal signal peptide (1–21-amino acids) and a propeptide domain (22–45-amino acids), which is removed post-translationally to release the mature BACE1 [23]. Mature BACE1 has two catalytic aspartic acid sites at amino acids 98 and 289, located at the extracellular domain. BACE1 activity is optimal at acidic pH; thus, it is more active in acidic compartments of the cell, such as the Golgi apparatus and endosomes of the endocytic pathway [23]. Within the cell, BACE1 localizes at the trans-Golgi network (TGN) and plasma membrane [24]. BACE1 is the main enzyme that cleaves APP at Asp^{+1} and Glu^{+11} site to release Aβ [23] and has been shown to modify other substrates that function in brain development, such as neuregulin and the β2 subunit of voltage-gated sodium channels (Nav1, β2) [25]. Various BACE1 knockout studies in mice implicate BACE1 in a variety of processes including memory, myelination in the peripheral nervous system, regulation of voltage-dependent sodium channels, cellular metabolism, growth, motor coordination, and axon guidance [22, 26]. BACE1 knockout mice also show aberrant phenotypes such as growth retardation, seizures, schizophrenia-like behaviors, and retinal pathology [26].

γ-Secretase is a protease complex composed of four subunits—PSEN1 or PSEN2 (the catalytic subunit of γ-secretase that contains two aspartyl residues), nicastrin (NCT), anterior pharynx defective (APH)-1a or APH-1b, and the presenilin enhancer-2 (PEN-2) which cleaves APP between the 37- and 43-amino acids of the Aβ region [22]. γ-Secretase/PSEN1 is generally found to be at the plasma membrane and the endosomal/lysosomal system but several studies have also detected PSEN1 at the endoplasmic reticulum (ER), trans-Golgi network (TGN), and Golgi or post-Golgi transport vesicles in cells [22].

APP and BACE1 Trafficking in Relation to Aβ Production

Nascent APP generated from the ER matures and undergoes several post-translational modifications as it travels towards the Golgi apparatus. These include *N*- and *O*-glycosylations, phosphorylation, sulfation, and endoproteolysis [15, 27, 28]. Upon reaching the cell surface, APP is internalized via clathrin-mediated endocytosis via recruitment by the adaptor-protein complex AP-2 and Dab2. After internalization, APP is either transported into the endosomes and then exocytosed to the plasma membrane or transported to the lysosomes for final degradation [15, 27, 29]. Only a small fraction of nascent APP is recycled back from the endosomes to the plasma membrane while the majority of it remains in the TGN and Golgi bodies [15, 28]. During the transport of APP to the cell surface and endocytosis, it undergoes

endoproteolytic cleavage either via α-secretase or BACE1 [27, 30].

Nascent BACE1 generated from the ER, as a ~70-kDa protein, fully matures through *N*-glycosylation and addition of sugar moieties, resulting in a ~75-kDa protein that is endo H resistant [27]. After leaving the ER, the N-terminal domain and pro-peptide domain of BACE1 are removed post-translationally [31]. It has a single transmembrane domain and a cytoplasmic tail containing an acidic domain that signals its transportation along the secretory pathway, as well as subcellular localization [27]. BACE1 generated from the ER is transported across the Golgi apparatus to the cell surface and re-internalized into the endosomes [24] or degraded in the lysosomes [32]. In the amyloidogenic pathway, some of the APP that has not been proteolytically processed at the plasma membrane is internalized and cleaved by BACE1 and γ-secretase, mainly in the TGN and endosomes [29]. Cell surface APP is preferentially processed via the non-amyloidogenic pathway as α-secretase competes with BACE1 at the plasma membrane [33]. Intracellular APP can also be processed through the amyloidogenic pathway [33] due to the presence of BACE1 and γ-secretase in acidic intracellular compartments (Fig. 1). A subsequent increase in APP internalization is likely to augment the co-residence of APP and BACE1 in the TGN or endosomes, increasing Aβ generation [29].

Protein-Protein Interactions Regulating Amyloidogenesis

APP trafficking is determined by its interaction with other proteins through its tyrosine-based motifs located at its cytoplasmic tail: YTSI, located 4-amino acid residues away from the transmembrane domain, as well as GYENPTY and YKFFE, located within the AICD region [33]. The YTSI motif is involved in mediating endocytosis [34]. The YENPTY motif is involved in re-internalization of APP from the plasma membrane through its interaction with AP-2 [35, 36] via Disabled-2 (Dab2), a protein containing a phosphotyrosine-binding (PTB) domain [33, 37]. The YKFFE motif is involved in the TGN-to-endosome transport of APP through binding with AP-4 [33, 38]. AP-1A, through binding with the GYENPTY, sorts APP to the cell surface while AP-1B that binds to the YTSO motif of APP sorts it from apical to basolateral membrane in epithelial cell line LLC-PK1 cells [39]. AP-3 also mediates APP trafficking from the Golgi to the lysosomes in SN56 cells by binding to the YTSI motif [35].

APP trafficking and processing are highly influenced by the binding of several adaptor proteins or modifications of its AICD. The AICD region contains binding site for adaptor proteins with PTB domains, such as the X11-family proteins. Some such proteins include Mint 1 (also called X11α), Mint 2 (or X11β), Mint 3, X11-like proteins (X11L), Fe65, Fe65L1, Fe65L2, density lipoprotein (LDL) receptor-related protein (LRP), mammalian disabled-1 (mDab1), c-Jun amino-terminal kinase-interacting protein (JIP1b, JIP2) family members, sorting nexins (SNX) [22, 40–42], and sortilin [43] (Fig. 2).

The binding of X11α and X11β to APP inhibits Aβ production in vitro and in vivo [40, 44–46] Studies on X11α knockout, X11L knockout, X11α/X11L double knockout, and X11L knockout in AD mouse models showed increase Aβ production [41]. APP associates with the protein complex X11-Munc18-syntaxin-1 in detergent-resistant membrane, which is devoid of BACE1 [40]. In the detergent-resistant membrane, X11-Munc18 is required by APP to associate with syntaxin-1-containing microdomain [47, 48], so when Munc18 is phosphorylated by Cdk5, APP switches from a X11-Munc18-syntaxin-1-containing domain to BACE1-containing microdomain, facilitating APP-BACE1 interaction and Aβ generation [40]. X11 proteins are also reported to retain APP at the ER, reducing Aβ generation [49, 50]. While overexpression of X11β in mice inhibits Aβ generation and delays amyloid plaque formation [46], the phosphorylation of X11β results in either reduction in Aβ secretion or increase Aβ generation [51]. Specifically, Src-dependent phosphorylation of X11β speeds up APP endocytosis and sorts it to autophagosomes, causing an increase in Aβ accumulation while Src-independent phosphorylation of X11β enhances APP recycling to the plasma membrane and amyloidogenic processing [51]. In addition, APP binding to ApoER2, mediated by X11α/X11β causes an increase in Aβ generation [52]. Mint3 transports APP from the TGN to the plasma membrane and when it is overexpressed in cells, significant Aβ is generated [42].

Fe65 binds to membrane-bound AICD [53, 54]. Overexpressing Fe65 results in increased Aβ release while its knockdown reduces Aβ secretion [55]. Upon binding, Fe65 forms a complex with Tip60, a nuclear complex with histone acetyl transferase activity, and MED12, a subunit located within the RNA Polymerase II transcriptional Mediator that regulates gene-specific transcription factors in the nucleus [54, 56–59]. AICD then increases the transcription of neprilysin (NEP), BACE1, and APP. NEP preferentially degrades $A\beta_{40}$ but not $A\beta_{42}$ [59]. The AICD transcriptional signal also activates the transcription of glycogen synthase kinase 3β (GSK3β)-mediating Tau hyperphosphorylation [60]. Thus, Fe65 increases the $A\beta_{42}/A\beta_{40}$ by modulating NEP transcription. Fe65 also associates with NFTs in AD and interacts with the N-terminal region of Tau-containing prolines that are phosphorylated via GSK3β and Cdk5 [61]. Fe65 possibly links Tau to APP as they all co-localize and form a complex in vivo in cerebellar granular neurons [61].

Fe65 also couples with LRP1, a multifunctional endocytosis receptor containing two NPXY motifs, facilitating APP

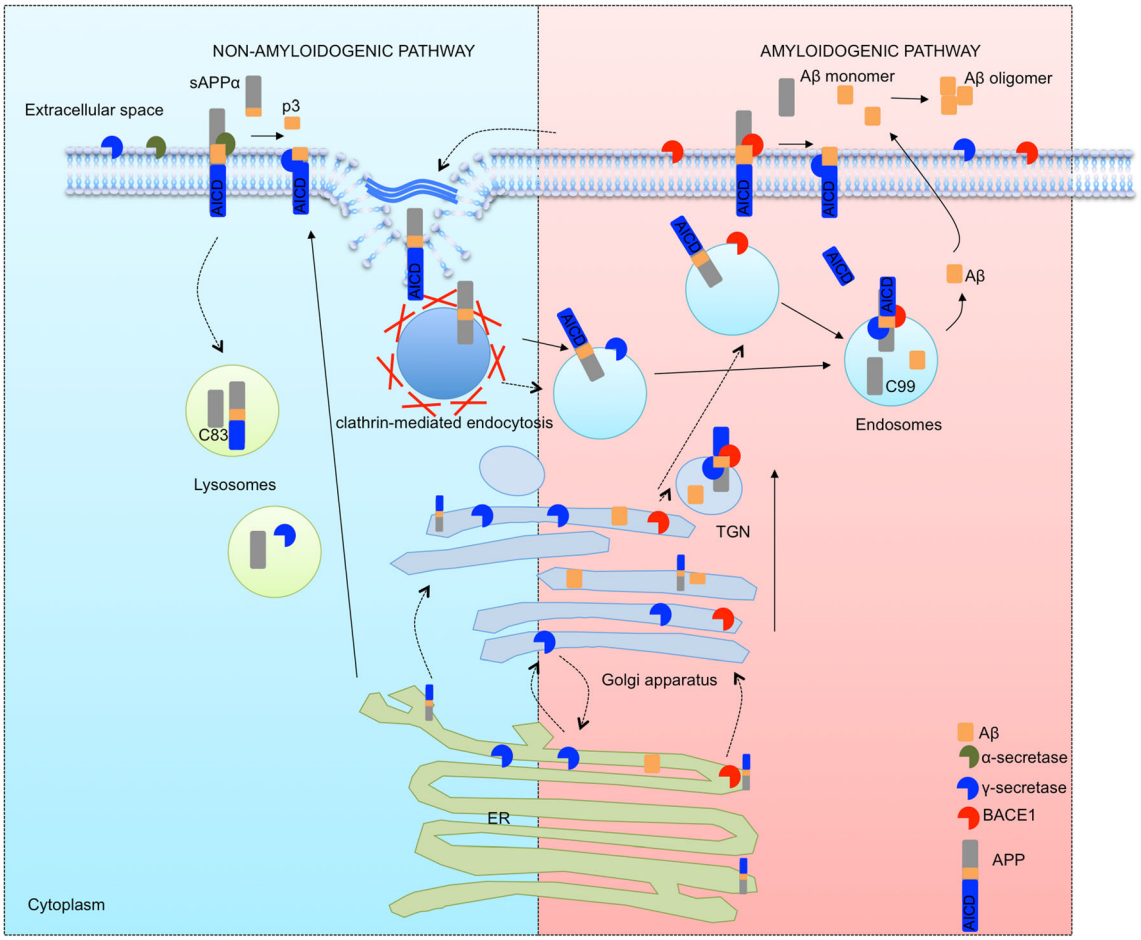

Fig. 1 APP and processing enzymes trafficking during amyloidogenesis. APP is generated from the endoplasmic reticulum (ER) and transported across the Golgi apparatus to the plasma membrane. APP at the plasma membrane is cleaved through the non-amyloidogenic pathway. Cleaved and uncleaved APP are internalized via clathrin-mediated endocytosis and fused with endosomes or degraded in the lysosomes. BACE1 is also generated at the ER, modified as it is transported from the Golgi to the plasma membrane and internalized into the endosomes. The γ-secretase complex formed at the ER is transported to the Golgi and back to the ER for a final quality check of the complex formation before it is transported to the plasma membrane. Most APP internalized into the endosomes and Trans-Golgi Network (TGN) is processed via the amyloidogenic pathway where most of the amyloid beta (Aβ) is generated

endocytic trafficking and subsequently modulating APP internalization and increasing Aβ generation [62–65]. Another homologous protein to LRP1, LRP1B, promotes the non-amyloidogenic processing of APP by retaining APP at the cell surface [66, 67]. Similarly, LRP10 functions in retaining APP at the TGN, preventing its amyloidogenic processing [68].

The NPTY motif of Dab1 associates with the PTB domain of APP [37]. When co-expressed with APP in COS7 cells, Dab1 promoted the α-secretase cleavage of APP by promoting its cell surface expression [37, 69]. Mammalian Dab1 also competes with Fe65 binding to LRP that results in the diminished APP-LRP complex formation and reduced level of APP and APP-CTF released in the cells [70]. This also affects the transport of AICD to the nucleus, as well as processing of APP [70].

JNK interacting proteins, JIP1b is also reported to bind APP at the GYENPTY motif [71, 72]. Upon binding, JIP1b stabilizes immature APP, resulting in the curtailment of the release of sAPPs from APP, CTF formation, and $A\beta_{40/42}$ generation [49]. However, JIP1b also induced phosphorylation of APP at Thr668 via JNK, the process that is mainly involved in inducing APP processing and Aβ generation [49].

APP binding with type-I transmembrane protein sorLA/LR11 facilitates trafficking of APP from the plasma membrane into retromer recycling endosomes to retrieve APP [14] and retains APP in the TGN, reducing APP processing [73, 74]. Sortilin, through its FLVHRY motif, binds to the NPTYKFFE motif within the AICD of APP and regulates the targeting of APP towards the lysosome and lipid rafts [43]. However, sortilin was also found to increases the α-secretase cleavage of APP and transport sAPP to lysosomes for degradation in neurons [75], which agrees to a previous study [43]. However, it is still unclear whether sortilin-mediated targeting of APP towards lipid raft leads to the amyloidogenic processing of APP. A recent study showed that knockout of sortilin in APP/PS1 transgenic mice significantly

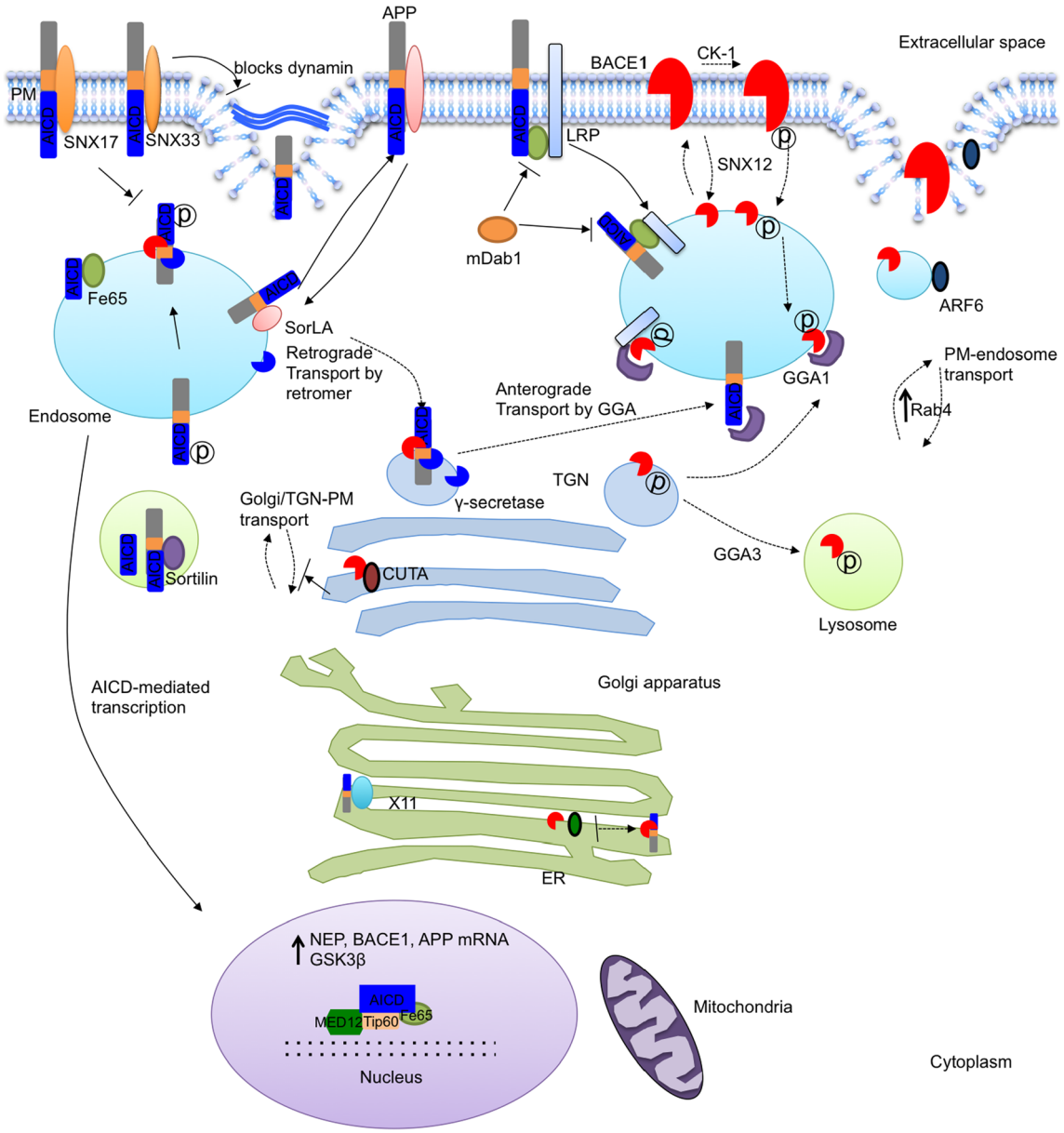

Fig. 2 APP and BACE1 trafficking and their interaction with adaptor proteins. APP and BACE1 interact with several adaptor proteins, regulating their trafficking in cells. Some of the known adaptor proteins that interact with the APP intracellular domain (AICD) are X11 family of proteins, Fe65, LRP, SorLA, mDab1, SNX17, and SNX33. AICD released from APP processing binds to Fe65 to activate the transcription of several genes such as neprilysin (NEP), APP, and BACE1, as well as GSK3β in the nucleus. This process occurs by binding with other proteins such as MED12 and Tip60. The phosphorylation of AICD at Thr668, either through PKC and JNK, aids APP-Fe65 binding. Fe65 binds APP and LRP, facilitating APP endocytosis when LRP is internalized. Mammalian Dab1 also binds to Fe65 and LRP and may compete for this binding with APP. Thus, APP-mDab binding inhibits the binding to Fe65 and LRP and the subsequent APP endocytosis. APP binding with SorLA, which facilitates the transport of APP between the cell surface and endosomes and retains APP at the TGN, results in increased Aβ generation. Fe65 also retains APP at the TGN, facilitating BACE1 cleavage. SNX17 and SNX33 stabilize APP at the cell surface supporting the non-amyloidogenic processing of APP. Knockdown of SNX17 results in increased APP endocytosis. SNX33 blocks dynamin, a key protein in clathrin-mediated endocytosis, inhibiting APP endocytosis. Similar to APP, the phosphorylation of BACE1 at Ser498 by CK-1, increases its retrograde transport from the cell surface towards the TGN while unphosphorylated BACE1 remains at the endosomes. During this transport, phosphorylated BACE1 also interacts with GGA1, LRP1 and SorLA which increase the trafficking of BACE1 to the TGN, increasing Aβ generation. Phosphorylated BACE1 binds GGA1 at the endosomes. Binding of BACE1 with GGA3 regulates its transport from the TGN towards the lysosomes for degradation. BACE1 internalization is also increased by ARF6 that facilitates the transport of BACE1 between endosomes and TGN. BACE1-CUTA binding reduces the transport of BACE1 from Golgi/TGN to the plasma membrane, increasing Aβ generation. In contrast, the overexpression of Rab4 facilitates BACE1 recycling from endosomes to the cell surface, reducing APP-BACE1 interaction at the endosomes. RTN3 stabilizes BACE1 at the ER, preventing it from accessing APP and also reducing Aβ generation

increased amyloidogenesis and amyloid plaques in the cortex and hippocampus [76]. An anatomical study shows that the C-terminal fragment of sortilin is highly co-localized with amyloid plaques in both human and transgenic AD mice, but the significance of this co-localization is not clear [77]. However, several studies have shown variations in the expression pattern of sortilin in AD [78–81].

APP interaction with SNX33 and SNX17 favor α-secretase cleavage and steady-state stabilization of APP, respectively. This leads to a reduction in Aβ production [63]. SNX33 binding with APP blocks the action of dynamin, a protein involved in the scission of vesicles from the plasma membrane; thus, APP is not endocytosed and remains at the plasma membrane and becomes available for α-secretase cleavage [82]. On the other hand, knockdown of SNX17 results in increased APP trafficking to the endosomes, increasing Aβ generation [37, 83]. The ectodomain of APP also binds to the ligand binding site of Nogo-66 receptor or NgR and causes the reduction of APP processing by either blocking the action of secretases or APP accessing the compartments where the secretases convene [84]. A summary of APP-interacting proteins is shown in Table 1.

BACE1 is also internalized through the interaction of its cytoplasmic tail with ADP-ribosylation factor-6 (ARF6) to RabGTPase 5 (Rab5)-positive early endosome [29, 96] and to clathrin-associated AP-2 complex [97]. ARF6 also mediates the recycling of BACE1 between the TGN and endosomes [29]. AP-2 binds and mediates the internalization of BACE1 from the plasma membrane to the endosomes [97]. BACE1 is also internalizes from the TGN to the endosomes through its interaction with Golgi-localized gamma ear containing ribosylation factor binding (GGA) proteins [24, 97]. GGA proteins, such as GGA 1, 2, and 3, are monomeric adaptors that sort cargo such as BACE1 from TGN to endo/lysosomal compartments [98]. The overexpression of GGAs reduced the secretion of APP fragments and Aβ as GGA proteins could retain APP at the Golgi and perinuclear compartments [99]. GGA1 interaction with LRP and LR11/SorLA also mediates the non-amyloidogenic processing of APP by enhancing the transport of BACE1 from endosomes to TGN [100]. The interaction of phosphorylated BACE1 with GGA3 determines its transport to lysosomes and proteasome for degradation [31]; therefore, silencing GGA3 will increase BACE1 levels and activity, and increase Aβ generation in AD [32].

The interaction of BACE1 with SNX family members such as SNX4, SNX6, and SNX12 also influences BACE1 trafficking. SNX4 expression in post mortem AD brains is altered [101]. In cells, the overexpression of SNX4 increases BACE1 levels and recycling from the plasma membrane to the endosomes, resulting in increased Aβ generation [101, 102]. SNX6 retains BACE1 at the endosomes and negatively regulates BACE1 cleavage of APP [103]. SNX12 modulates BACE1 trafficking between the cell surface and endosomes, increasing BACE1 cleavage of APP [104]. Increased localization of BACE1 at the endosomes would enhance its association with APP. The overexpression of Rab4, which mediates recycling of molecules between endosome and plasma membrane, reduces Aβ generation as it reduces APP-BACE1 interaction at the endosome [29].

BACE1 also partners with reticulon/Nogo proteins such as reticulon 3 (RTN3). When RTN3 is overexpressed in cells, BACE1 retention at the ER is increased [105]. As a result, BACE1 has reduced access to APP, thus Aβ generation is also reduced [106]. Retromer complexes, VPS35 and VPS26 bind to BACE1 promotes BACE1 transport from the endosome to Golgi [107]. Reduction in the expression of these proteins results in increased localization of BACE1 with APP at the endosomes [63, 108]. The interaction with CutA divalent cation tolerance homolog (CUTA) reduces the transport of BACE1 from Golgi/TGN to the plasma membrane, increasing Aβ generation [63, 109]. Sortilin also binds and promotes BACE1 retrograde trafficking and modulates BACE1-cleavage of APP [78]. The summary of BACE1 trafficking influenced by selected adaptor proteins discussed is shown in Fig. 2 and a summarized list of BACE1-interacting proteins are shown in Table 2.

Protein Modifications in APP and BACE1 Regulating Amyloidogenesis

The phosphorylation of AICD at particular sites (Thr654, Thr668, Tyr682, and Ser655 (APP_{695} numbering) alters the conformation of the cytoplasmic tail, modifying its signaling and interaction with adaptor proteins and other kinases and thus influences APP processing [34, 95, 110]. The phosphorylation at Thr654 by Rho-associated, coiled-coil containing kinase 2 (ROCK2) enhances the γ-secretase cleavage of CTFβ while the phosphorylation of AICD at Ser655 by protein kinase C (PKC) modulates APP endocytosis and amyloidogenic processing [111]. Thr668 phosphorylation, which shifts the *cis/trans* conformation of the prolyl bond, interferes with APP binding to its physiological adaptor proteins such as Fe65, Mint1, and Mint2 [22, 110]. Thr668 phosphorylation is necessary for AICD-Fe65 binding and subsequent transport of AICD towards the nucleus [60]. APP phosphorylated at Thr668 have been found to co-localized with phosphorylated Tau in neurons and preferentially associates with BACE1 in the endosomes in cultured primary neurons, favoring amyloidogenesis [112]. Another adaptor protein, Pin1, also binds to the phosphorylated APP at Thr668 and equilibrate the *cis* and *trans* isomer of APP Thr668, [94]. When Pin1 is overexpressed, it reduces Aβ secretion and if knockout, it reduces Aβ secretion [94]. Several Src homology 2 domain (SH2) domain-containing proteins and PTB-

Table 1 APP-interacting proteins

Name	Motif/Region in APP	Motif in the protein	Function	Method of detection	Ref.
AP-1(A) AP-1(B)	$GY^{682}ENPTY^{b}$ $Y^{653}TSI^{b}$	μ1A subunit μ1B subunit	Mediates protein transport between TGN and endosomes. Involved in APP sorting to the cell surface. Sorts APP from apical to basolateral membrane in LLC-PK1 cells	In vitro binding assay, Co-IP. Co-localization, knockdown assay	[35, 39, 85]
AP-2	$Y^{682}ENPTY$	α1, α2, β subunits	Mediates clathrin-mediated endocytosis of APP	Peptide pull down; mass spectrometry; Co-IP extracted ion chromatogram (XIC) label-free quantification using LC-MS/MS	[35, 36]
AP-3	$Y^{709}TSI^{712a}$	δ subunit	Transport APP from Golgi to lysosome in SN56 cells	In situ proximity ligation assay	[35]
AP-4	YKFFE	μ4 subunit	Transport APP from the TGN to endosomes	X-ray crystallography; co-localization; metabolic labeling, pulse-chase analyses	[38, 86]
Dab1	NPTY	PTB	Dab1 expression promotes α-cleavage of APP, increases cell surface expression of APP	GST pull-down assay yeast 2-hybrid, Co-IP; X-ray crystallography, cell surface biotinylation	[37, 69]
Dab2	GYENPTY	PTB	APP may interact directly with AP-2 via Dab2; mediates APP endocytosis	GST pull-down assay	[33, 37]
Fe65	YENPTY	PTB	Forms a complex with AICD and Tip60 to regulates APP transcription	GST-binding assay; Co-IP	[37, 45, 54, 57]
X11 proteins	$G^{681}YENPTY^{687}$	PTB	Suppress the translocation of APP into BACE- and γ-secretase-rich DRM domains.	GST-binding assay; Co-IP	[37, 45]
X11α (APBA1/MINT1)	-YENP-		X11α/β mediates protein complex formation of APP and LRP8/ApoER2, facilitating endocytosis of these proteins leading to ApoE-induced Aβ production. Directly interacts with APP to inhibit Abeta40 and Abeta42 secretion[c]		[52, 44]
X11 β (APBA2/MINT2)	-YENP-	PTB	Phosphorylation of Mint2 accelerates APP endocytosis and sorts APP predominantly to autophagosomes, that may enhance intracellular and extracellular Aβ accumulation and reducing Aβ secretion	In vitro phosphorylation; cell surface biotinylation; internalization and recycling experiment; ELISA	[51]
Mint3/X11γ	-YENP-	PTB	APP and Mint3 colocalize at the late Golgi/TGN. Sorts and basolaterally directs the exit of APP from the Golgi.	Optiprep density sedimentation; immunomagnetic isolation with antibodies	[42]
SNX17	NPXY/NXXY	Phox-homology (PX) domain	Important in APP stability and cell surface localization.	GST pull-down assay	[37, 83]
SNX33	nd	Binds to dynamin	Inhibits dynamin-dependent endocytosis, thus when it is expressed, it inhibits APP endocytosis, increasing APP cell surface level and α-cleavage.	Expression cloning screen; immunofluorescence-based anti-APP antibody uptake assay; Co-IP	[82]
LRP1	NPXY	-NPTYATL-; within the intracellular domain	LRP1 associates with APP via Fe65, forming a tricomplex, mediating its internalization and β-processing.	In vitro translation and glutathione *S*-transferase pull down; Co-IP	[62–65]
LRP1B	KPI-containing domain	Domain IV	LRP1B retains APP at cell surface, decreases APP amyloidogenic processing	Co-IP; continuous degradation assay	[67, 87]
LRP10	N-terminal domain				[68]

Table 1 (continued)

Name	Motif/Region in APP	Motif in the protein	Function	Method of detection	Ref.
		Cytosolic domain (DXXLL)	LRP10 traffics from TGN to PM, gets internalized towards the endosomes and recycles back to TGN. It retails APP at the TGN, protecting APP from amyloidogenic processing.	Co-IP; GST pull-down assay; antibody uptake assay; cell surface biotinylation; pulse chase assay	
SorLA	nd	Ectodomain	Confines APP to Golgi compartments and impairs transport to the cell surface and proteolytic processing	Surface plasmon resonance analysis; sedimentation equilibrium technique; subcellular fractionation; Co-IP; FLIM	[88]
JIP1b	GYENPTY	SH3, PI	Modulates APP phosphorylation at Thr-668 residue via JNK activation. Enhances APP anterograde transport in neurons.	Yeast 2-hybrid screening; Co-IP; in vitro protein binding assay	[49, 71, 72]
P75NTR	N-terminal region sAPPα, sAPPβ, and Aβ	ECD	P75 binding with sAPPα promotes neurite outgrowth. P75 binding with Aβ promotes apotosis. P75 binding with APP and BACE1 induces their internalization and endosome localization promoting amyloidogenesis.	Pull-down assay; Co-IP; ELISA	[9, 89–93]
Sortilin	Extracellular 6A domain; NPTYKFFE	Extracellular domain; carboxyl-terminal F/YXXXXF/Y	Intracellular localization of APP is independent of sortilin but targets sAPP for lysosomal degradation, sortilin might selectively increase α-secretase cleavage, regulates APP lysosomal and lipid raft trafficking through FLVHRY motif	Immunoprecipitation, proximity ligation assay; FRET; Co-IP	[43, 75]
NgR	Amino and carboxyl segments of the ectodomain of APP	Leucine-rich repeat ligand-binding domain	NgR/APP interaction suppresses amyloidogenesis by reducing a and b-secretases cleavage and reducing the access of APP to cellular compartments.	IP; covalent cross-linking assay	[84]
Pin1	APP Thr-668 site	WW domain	Pin1 overexpression reduces Aβ secretion while its knockout increases Aβ generation	GST pull down; NMR spectroscopy	[94]
ShcA, ShcB, Grb7, Grb2, Nck	$Y^{682}ENPTY^{687}$	PTB, SH2	May facilitate dimer or heteromer formation between APP proteins and APP family induced by APP-Tyr682 phosphorylation	In vitro protein pull-down assay	[95]

nd, not determined

[a] (APP751 numbering)

[b] app695

Table 2 BACE1-interacting proteins

Name	Motif/region in BACE1	Motif in the protein	Function	Method of detection	Ref
AP-2	DDISLL	α-σ2 hemicomplex	Directly binds BACE1 and mediates its internalization from the PM via clathrin-mediated endocytosis.	Yeast 3-hybrid (Y3H) system	[33, 97]
ARF6	DISLL	nd	Sorts BACE1 from transient pre-endosomal compartment to early endosomes	Immunostaining; immunoblotting; metabolic labeling	[29, 96]
SNX4	nd	nd	SNX4 direct interaction with BACE1 increases its steady-state level and recycling from the endosome to the PM, resulting in increased Aβ generation.	Coimmunoprecipitation gradient fractionation	[101]
SNX6	nd	Phox homology (PX domain: aa 172–406), BAR domain (aa 1–176)	Negatively modulates the endosome to TGN trafficking of BACE1 and its knockdown increase bace1-mediated cleavage of APP	In-cell chemical cross-linking; tandem affinity purification; Co-IP	[103]
SNX12	nd	PX domain	Downregulation of SNX12 accelerates BACE1 endocytosis and decreases steady-state level of cell surface BACE1	Co-IP; cell surface biotinylation; Ab, BACE1 assays	[104]
GGAs	DISLL acidic motif	GAE domain	GGAs regulate BACE1 anterograde trafficking from TGN to endosomal/lysosomal system.	Co-IP; in vitro Co-IP	[24, 99]
Rab4	DISLL acidic motif	nd	Rab4 mediates the recycling BACE1 between the plasma membrane and endosomes and sorting from the endosomal/lysosomal pathway to recycling endosomes	Antibody internalization assay; knockdown experiments	[29, 102]
Sortilin	nd	YSVL motif	Binds to BACE1 and GGAs. Mediates the retrograde trafficking of BACE1	Co-IP	[78]
Reticulon family (RTN1, RTN2, RTN3, RTN4)	nd	nd	Interacts with BACE1 and decreases both BACE1-mediated cleavage of APP and Aβ production.	IP, matrix-assisted laser desorption ionization (MALDI) mass fingerprinting methods	[105]
Retromer complex (VPS35/VPS26)	nd	The amino acids of 390–606	Promotes BACE1 endosome-to-Golgi retrieval, inhibiting BACE1 activation.	Co-IP, GST pull-down assay	[107]
CUTA	H component of the N-terminal domain	β-site	Knockdown of CUTA can reduce and increase BACE1-mediated APP processing/Aβ secretion. RNA interference of CUTA decelerates intracellular trafficking of BACE1 from the Golgi/trans-Golgi network to the cell surface and reduces the steady-state level of cell surface BACE1	Co-IP	[109]

containing proteins binds APP at the phosphorylated Tyr682 sites and have been described in another publication [95].

The retrograde transport of BACE1 is also influenced by the phosphorylation of its amino acid serine 498 (Ser498), via casein kinase 1 (CK-1) activity [98]. In its phosphorylated form, BACE1 is retrogradely transported from the cell surface to the TGN. During this transport, BACE1 associates with GGA proteins at the endosomes using its cytoplasmic domain motif DXXLL [24, 113]. Non-phosphorylated BACE1, on the other hand, is reported to accumulate at the endosomes and is recycled directly from the endosomes to the cell surface [24]. The mutation of the S498 residue results in the accumulation of BACE1 at the endosomes, enhancement of BACE1 recycling from endosome to the cell surface, and inhibition of interaction between BACE1 and GGA1. These findings suggest that disruption in the phosphorylation of BACE1 leads to enhanced Aβ generation because of its retention in the endosomes [24, 98, 100].

Although BACE1 phosphorylation of Ser498 appears to favor non-amyloidogenic processing of APP, the presence of mutant APP, such as in AD mouse models, could change the trafficking or subcellular localization of APP and BACE1, with an optimum pH not permitting BACE1 cleavage of APP [100]. The increase in $A\beta_{42}$ also increases BACE1 levels, which further increase APP amyloidogenic processing in a positive feedback loop [31]. Thus, it is important to investigate the changes incurred by Ser498 phosphorylation in APP processing under pathological conditions. Aside from phosphorylation, BACE1 is also *S*-palmitoylated on four cysteine residues at the junction of the TM and cytosolic domain and transported to lipid rafts where β-processing of APP is also enhanced, whereas non-palmitoylated BACE1 translocates to non-raft domains [106].

Neurotrophin-Mediated Amyloidogenesis

Neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT3, and NT4 are a family of growth factor proteins [114, 115] that support neural development, maintenance of the adult nervous system, synaptic plasticity, and learning and memory [116]. Further details on the function of these neurotrophins are found in reviews [115, 117]. Neurotrophins are initially synthesized as pro-neurotrophins and are subsequently converted to mature forms. There are proNGF, proBDNF, proNT3, and proNT4. The major receptors for these neurotrophic factors include $p75^{NTR}$ and tropomysin-related kinase/tyrosine receptor kinase (Trk) receptors A, B, and C (TrkA, TrkB, TrkC) [118]. Pro-neurotrophins preferably bind to $p75^{NTR}$/sortilin, triggering death signaling in cells, while mature neurotrophins predominantly interact with Trk receptors, promoting cell growth and survival [116, 119–121].

In one study, NGF has been shown to promote the binding of TrkA to APP and facilitate APP trafficking to Golgi, resulting in the reduction of APP exposure to BACE1 cleavage and generation of Aβ in basal forebrain neurons of mouse [122]. The APP-binding site where TrkA interacts contain the α- and β-secretase-binding site, thus NGF-mediated modulation of TrkA-APP promotes the non-amyloidogenic processing of APP [123]. NGF also controls the phosphorylation of APP at Thr668, a key modification that also control APP trafficking. NGF withdrawal using anti-NGF antibody results in the increase of APP Thr668 levels in PC12-derived neurons while exposure to NGF reduces APP Thr668 levels in rat primary neurons [122]. proNGF has been found to be upregulated and mediates neurodegeneration in AD [124–126].

Sortilin and $p75^{NTR}$ both interacts and facilitate the trafficking of APP and BACE1 [9, 43, 78, 89, 127], thus these two receptors have a significant role in amyloidogenesis. There are contradicting findings on whether sortilin and p75 increase or decrease Aβ production or whether these two receptors are good or bad molecules. For instance, sortilin expression have been reported to be either upregulated or downregulated in AD [78–80]. It has also been found unchanged in post-mortem brains with mild cognitive impairment and AD [81]. Sortilin downregulation have also been reported to decrease sAPPα levels by promoting α-secretase cleavage of APP [75]. The intracellular domain of Sortilin also interacts with APP, mediating APP non-amyloidogenic processing, lysosomal processing and lipid-raft localization [43, 75]. In contrast, the interaction of the cytoplasmic tail of sortilin with BACE1 regulates BACE1 retrograde trafficking and recycling between endosomes and the TGN, potentially resulting in increased Aβ generation. Thus, there is a possibility that $p75^{NTR}$ and Sortilin could direct BACE1-mediated cleavage of APP when they are bound together in the presence of neurodegenerative ligands, but this requires further investigation.

On the contrary, an increase in $A\beta_{40}$ accumulation in 5 and 9 months $Sort^{-/-}$/PDAPP (APP^{V717F}) mice and in 2 months old but not in 10 months old $Sort^{-/-}$/5xFAD mice has also been reported [128]. Our group has also found that sortilin is elevated in APP/PS1 transgenic mice and knocking sortilin also resulted in the increase of $A\beta_{40}$ levels [79]. Moreover, our group also determined that sortilin promotes APP degradation by mediating its transport to the lysosomes [43]. With sortilin deletion, APP levels were elevated and allowed subsequent processing by BACE1, resulting in increase Aβ generation. Therefore, an increase in sortilin expression in AD could potentially promote the amyloidogenic processing of APP as sortilin facilitates APP escaped from degradation. The conflicting results in the previous studies mentioned could be due to several factors such as the different transgenic mice model used, the protein tag of the sortilin plasmid used that could have interfered with the other adaptors of sortilin and altered its physiological subcellular localization, and the

presence of any artifacts caused by the method of overexpressing sortilin and subsequent knockdown using shRNA could be present.

Different groups have reported conflicting results about $p75^{NTR}$ expression. Upregulation of $p75^{NTR}$ expression in the nervous system following injury [129, 130], cellular stress [131], seizures [132], aging [133, 134], and in AD [135–138] have been reported. $p75^{NTR}$ levels were elevated in the CA1 and CA2 subfields of the hippocampus [135] and cortical neurons [136] of AD patients. Similar observation was found in two aged AD models, 3xTg-AD ($APP_{SWE}/PS1^{M146V}$/tau P301L) and APP^{SWE}/PS1dE9 [138]. In the latter model, $p75^{NTR}$ expression was elevated in the degenerative neurites of the cortex and hippocampus [137]. However, other reports also showed that $p75^{NTR}$ expression was reduced in the neurons at the nucleus basalis of Meynert (NbM) in AD patients [139, 140]. In some other research, $p75^{NTR}$ mRNA appeared normal or unchanged in the basal forebrain of AD patients [141–143]. The discrepancy in $p75^{NTR}$ expression observed in AD could be due to the different brain regions used in detecting the protein and the method of detecting it. A reduction in $p75^{NTR}$ expression could also be expected since it is mainly expressed in cholinergic neurons, which degenerate early in AD [144]. The elevated levels of Aβ also induced $p75^{NTR}$ and sortilin expression, and neurodegenerative signaling mediated by these two receptors [80, 90, 138]. In addition, Aβ could further induce neurodegeneration via activation of RhoA through $p75^{NTR}$ [116]. Moreover, $p75^{NTR}$ also partners with sortilin to mediate cell death signaling in cholinergic neurons [80, 145] mediated by their binding to proneurotrophins [146, 147]. Sortilin is required for $p75^{NTR}$-mediated pro-apoptotic signal [148]. Sortilin binds $p75^{NTR}$ at its juxtamembrane stalk (Thr228-Asp250) located extracellularly and mediates $p75^{NTR}$ shedding and cell death signaling [146]. Together, these two receptors bind proNGF, forming a tripartite complex [148, 149]. It is still unclear how the $p75^{NTR}$-sortilin complex would associate with APP and BACE1 and requires further investigation. Since both receptors bind and facilitate the amyloidogenic processing of APP, $p75^{NTR}$, and sortilin could be a perfect target for developing therapeutic drugs.

Further investigations on the role of $p75^{NTR}$ in AD have focused on examining its expression in post-mortem brain or using knockout animals. A study conducted on a select religious order of people investigated the relationship of $p75^{NTR}$ immunoreactivity at the NbM and the cognitive performance of the sample group with either non-demented, with MCI and with AD [150]. In this study, the reduction of $p75^{NTR}$ in MCI and AD cases was positively correlated with select measures of working memory and attention based on the mini-mental state examination and Global Cognitive test.

Several studies have showed conflicting conclusions about the function $p75^{NTR}$ in the cognitive behavior of mice. Two existing model for $p75^{NTR}$ knockout mice have been used in AD study. The first mouse model that has target deletion of exon III in $p75^{NTR}$ locus, resulting in the generation of a shorter isoform of $p75^{NTR}$ lacking the neurotrophin binding site ($p75^{NTR/ExonIII-/-}$ or p75KO) [151] and the second model has target deletion of exon IV that completely delete the full-length $p75^{NTR}$ [152]. Several studies have shown that p75KO mice compared with a wild-type control mice (129Sv) have improved spatial learning based on Barnes maze test, enlarged but reduced cholinergic neurons, and have enhanced long term potentiation at the hippocampus [153, 154]. However, another study showed that partial ($p75^{NTR}$ Exon III deletion) and complete deletion of $p75^{NTR}$ ($p75^{NTR}$ Exon IV deletion) resulted in increase in number of cholinergic neurons [155], thus improvement of mice cognitive behavior could be expected as found in previous studies [153, 154]. A recent study also showed that the in vivo knockdown of $p75^{NTR}$ could improve cognition by enhancing choline acetyltransferase activity at the hippocampus of Sprague-Dawley rats [156]. Although recent studies support the improvement of cognitive behavior when $p75^{NTR}$ is knocked out, the study by Peterson et al. showed that p75KO mice have impaired cognitive behavior and poor memory retention that is accompanied by the loss of cholinergic neurons [157]. Greferath et al. had attributed the discrepancy in the result of the behavioral studies to the slight difference in genetic background of the control used [153]. Peterson et al. group have used mice with a mixed gene of 129Sv/Balb/c, which could have an unknown characteristic while the other studies have used only a 129Sv with 95% locus similarity [153, 157]. Therefore, we have investigated the function of $p75^{NTR}$ in AD by knocking it out from APP_{SWE}/PS1dE9 mice, maintaining the purity of the genetic background to be the 129Sv strains [137]. However, we did not find any significant change in the cognitive behavior of APP_{SWE}/PS1dE9/p75KO mice compared with APP_{SWE}/PS1dE9 and even in p75KO compared with wild type up to 9 months of age. Despite the unchanged cognition in the mouse models studied, we were able to show that $p75^{NTR}$ deletion significantly reduced the levels of soluble Aβ in the brain and serum of mice but increased the accumulation of insoluble Aβ and amyloid plaque [137]. Interestingly, we also found that the recombinant extracellular domain of $p75^{NTR}$ (p75ECD) prevented the fibrillation and oligomerization of synthetic Aβ in cultured cells and reduced Aβ plaque in vivo [137]. The extracellular domain of $p75^{NTR}$ is shed from the simultaneous cleaving action of tumor necrosis factor α convertase, TACE, and γ-secretase [158, 159]. At physiological condition, the extracellular domain of $p75^{NTR}$ is expressed in different brain regions and increased with age in wild type mice [160]. While in AD, it is significantly reduced in the parietal cortex and cerebrospinal fluid of AD patients compared with age- and gender-matched non-demented people while the full-length $p75^{NTR}$ increased [160].

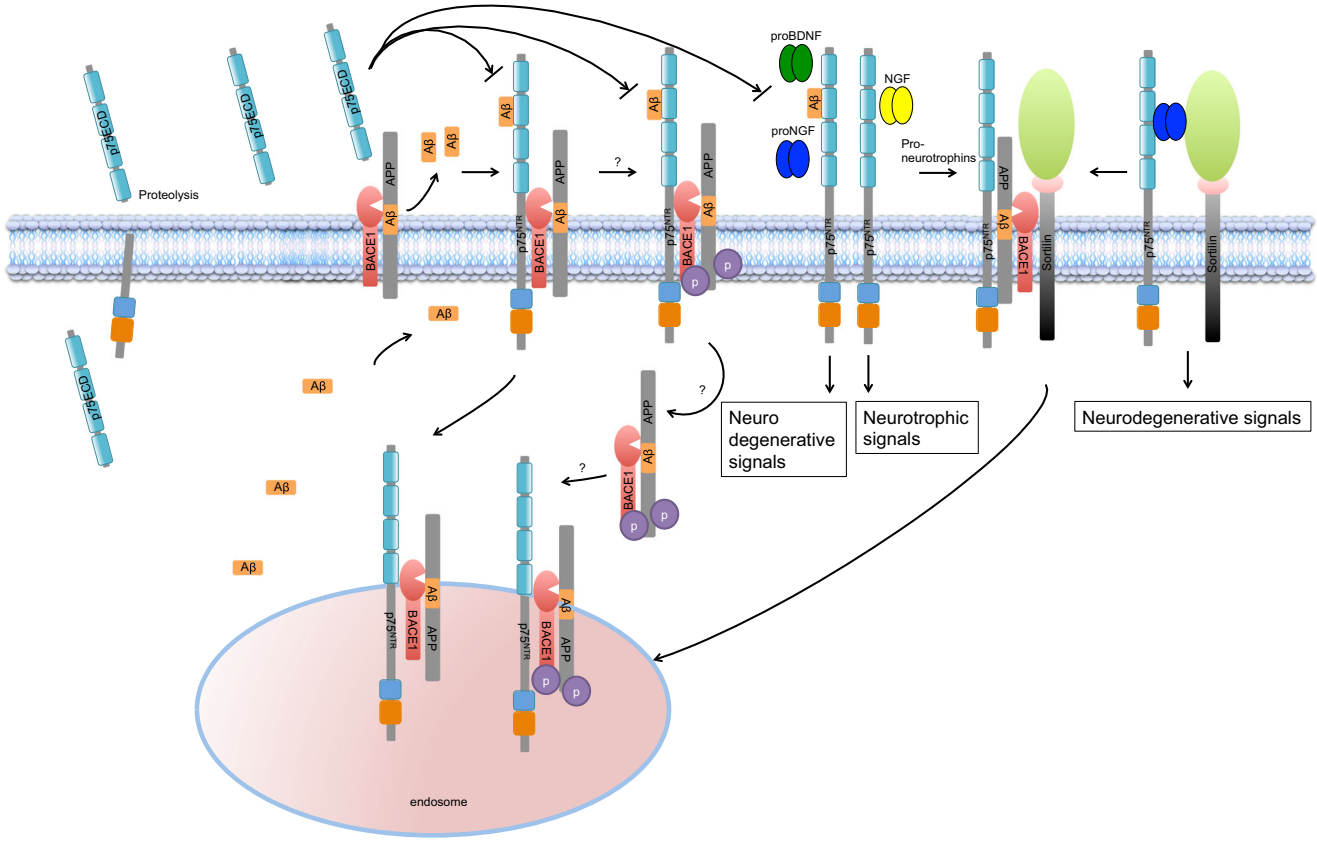

Fig. 3 Role of $p75^{NTR}$ in amyloidogenesis. In our proposed model, the increased generation of Aβ and neurodegenerative ligands (e.g., proNGF) in AD increases $p75^{NTR}$ expression and its interaction with APP and BACE1. $p75^{NTR}$ also induces the phosphorylation and internalization of APP and BACE1 towards the endosomes, enhancing Aβ generation. Proneurotrophins also enhance p75NTR-sortilin formation and mediates APP amyloidogenic processing at the endosomes. This cycle repeats itself and further promotes amyloidogenesis

In our previous study, we found that utilizing the recombinant p75ECD as a therapeutic agent could abolish amyloidogenesis in AD transgenic mice by inhibiting BACE1 expression and Tau hyperphosphorylation, as well as attenuating neuronal degeneration, astrogliosis and microgliosis in AD transgenic mice brains [160]. We have also found that p75ECD can block Aβ-induced phosphorylation of APP and BACE1 [9]. p75ECD has a highly negative net charge of − 24, causing it to have high affinity to many types of ligands and proteins, affecting their internalization and transport [158]. The recombinant p75ECD could disrupt the binding of Aβ with full-length $p75^{NTR}$, preventing Aβ aggregation and Aβ-induced neurotoxicity [137]. Recent reports have also showed that small molecule $p75^{NTR}$ ligand LM11A-31 effectively prevented and reversed the pathological processes in AD such as tau hyperphosphorylation and misfolding, cholinergic neurons degeneration, and cognitive impairments in AD mice [161, 162]. However, $p75^{NTR}$ function not only in mediating neurodegenerative signaling but also neurotrophic signaling and is determined by the type of ligands interact with the receptor and the cell type [144]. $p75^{NTR}$ binds to several molecules including APP and Aβ. The interaction of $p75^{NTR}$ with sAPPα promotes neurite outgrowth [89, 127]. Without the ligand-binding site, $p75^{NTR}$ does not bind Aβ, suggesting that the full-length also has some protective role against oligomeric Aβ-induced neurodegeneration [163]. Another study has also shown that $p75^{NTR}$ mediates $Aβ_{40}$ internalization and trafficking to the lysosomes for degradation [116, 164] while the binding of $p75^{NTR}$ with Aβ promotes neurodegenerative signaling [91, 92]. So, we have investigated other mechanism on how $p75^{NTR}$ drives amyloidogenesis. We have conducted co-immunoprecipitation, co-localization, and phosphorylation studies [9], which demonstrated that $p75^{NTR}$ interacts with BACE1. We also confirmed that $p75^{NTR}$ interacts with APP, which is induced either by Aβ or proNGF. $p75^{NTR}$ also enhances the internalization of both APP and BACE1 and their convergence at the endosomes and this could be further stimulated by Aβ [9]. Using p75KO mice, we found that $p75^{NTR}$ expression is required for the Aβ-induced phosphorylation of APP at Thr668 and BACE1 at Ser498 and Aβ generation in primary cortical neurons [9].

Another interesting molecule to investigate is the soluble protein α2-macroglobulin (α2M), an endoproteinase inhibitor, which have been found to increase $p75^{NTR}$'s production

and bind both $p75^{NTR}$ and proNGF [165]. α2M function in capturing and binding proteinases, polypeptides growth factors, and cytokines [166]. α2M expression is upregulated in the neuritic neurites in AD brain and binds Aβ with high affinity [166, 167] and prevents Aβ fibril formation [168] and mediates Aβ degradation and clearance [169, 170]. α2M complexes with NGF but negatively modulates TrkA activity and results in lack of trophic support while binding with proNGF protecting the latter from proteolysis, tipping the balance of NGF and proNGF in the brain [165]. The α2M–proNGF complex, which is more effective than free proNGF, binds $p75^{NTR}$ and mediates tumor necrosis factor-alpha production and $p75^{NTR}$-induced neurotoxicity [165]. Now, it is important to consider the ratio of NGF and proNGF in the brain especially in AD. According to the neurotrophic imbalance theory, the imbalance between mature neurotrophin and proneurotrophin signaling can lead to neurite collapse and cell death and drive downstream signaling pathways causing AD [145, 171, 172]. Others have supported that the trophic support by NGF is anti-amyloidogenic [173, 174]. For instance, elevated levels of proNGF in the brain would activate the neurodegenerative signaling mediated by $p75^{NTR}$ and sortilin while a high NGF level would increase $p75^{NTR}$'s affinity to mature neurotrophins and activate cell survival, growth and synaptic plasticity [175]. NGF has also been shown to increase the affinity and binding of TrkA to APP, which is otherwise inhibited by $p75^{NTR}$ [123, 176] potentially decreasing the amyloidogenic processing of APP.

Based on our findings and the work of other groups, we propose a mechanism of how $p75^{NTR}$ mediates amyloidogenesis (Fig. 3). In AD, where levels of Aβ and other neurodegenerative ligands are elevated, $p75^{NTR}$ becomes highly expressed and binds to both soluble and aggregated forms of Aβ. An increase in proneurotrophins could also activate $p75^{NTR}$-sortilin signaling, modulating the amyloidogenic processing of APP, possibly by forming complex with the two molecules. $p75^{NTR}$ interacts with APP [148] and BACE1 [9], inducing their internalization towards the endosomes, and induces their phosphorylation [9]. The combination of these signaling pathways eventually lead to further APP processing by BACE1 and subsequent Aβ generation. Thus, $p75^{NTR}$ mediates the feed forward function of Aβ in amyloidogenesis.

Conclusion

On the basis of APP and BACE1 trafficking, it is clear that the co-segregation of these molecules in the same compartments modulates APP cleavage by BACE1, resulting in Aβ production. Cellular compartments that have acidic pH optimal for BACE1 activity, such as the endosomes and TGN, are the main sites for Aβ generation. Most of APP adaptor proteins such as Fe65, SorLA, and LRP cause APP to undergo amyloidogenic processing at these compartments while APP binding to SNX17, SNX33, mDab1, and X11 proteins enhances non-amyloidogenic processing. In a similar manner, the interaction of BACE1 with GGA1, ARF6, SNX12, and CUTA increases its association with APP, increasing Aβ generation. Rab4, GGA3, SNX6, RTN3, VPS26, and VPS35 reduce APP-BACE1 interaction, thereby reducing Aβ generation. Thus, the co-residence of APP and BACE1 regulated by the several other adaptor proteins at the endosomes is a key factor in APP amyloidogenic processing. We found that $p75^{NTR}$ is required for APP and BACE1 to converge at the endosome. Given that several factors also enhance the generation of intracellular Aβ, it is worthwhile to determine the upstream molecular pathways that control the binding of APP and BACE1 with the different molecules known to increase APP and BACE1 endocytosis and co-residence. The trophic support provided by neurotrophins also facilitates non-amyloidogenic processing of APP while proneurotrophins modulate the amyloidogenic processing of APP through $p75^{NTR}$ and sortilin. We propose that pathological amyloidogenesis is regulated by Aβ, and proneurotrophin to $p75^{NTR}$ binding which regulates the convergence and endocytosis of APP and BACE1. However, further investigation is needed to confirm the formation of p75NTR-sortilin-APP-BACE1 complex within the cells especially in the endosome to validate our proposal. Moreover, we still need to determine the upstream factors that drive the modulation of amyloidogenesis via neurotrophins, neurotrophin receptors, as well as the possible cross-associated among APP and BACE1 adaptor proteins and $p75^{NTR}$ interactors.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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