PORTLAND PRESS

Review Article

Amyloid precursor protein and its interacting proteins in neurodevelopment

Dennis Dik-Long Chau, Laura Lok-Haang Ng, Yuqi Zhai and ⓘ Kwok-Fai Lau

School of Life Sciences, Faculty of Science, The Chinese University of Hong Kong, Hong Kong SAR, China

Correspondence: Kwok-Fai Lau (kflau@cuhk.edu.hk)

OPEN ACCESS

Amyloid precursor protein (APP) is a key molecule in the pathogenesis of Alzheimer's disease (AD) as the pathogenic amyloid-β peptide is derived from it. Two closely related APP family proteins (APPs) have also been identified in mammals. Current knowledge, including genetic analyses of gain- and loss-of-function mutants, highlights the importance of APPs in various physiological functions. Notably, APPs consist of multiple extracellular and intracellular protein-binding regions/domains. Protein–protein interactions are crucial for many cellular processes. In past decades, many APPs interactors have been identified which assist the revelation of the putative roles of APPs. Importantly, some of these interactors have been shown to influence several APPs-mediated neuronal processes which are found defective in AD and other neurodegenerative disorders. Studying APPs–interactor complexes would not only advance our understanding of the physiological roles of APPs but also provide further insights into the association of these processes to neurodegeneration, which may lead to the development of novel therapies. In this mini-review, we summarize the roles of APPs–interactor complexes in neurodevelopmental processes including neurogenesis, neurite outgrowth, axonal guidance and synaptogenesis.

Introduction to amyloid precursor protein

Amyloid precursor protein (APP) is one of the major interests in current research on Alzheimer's disease (AD) since the aberrant processing of APP contributes to the generation and accumulation of neurotoxic peptide amyloid-β (Aβ). Apart from its significant relevance in AD pathogenesis, APP also participates in various cellular activities which facilitate brain development and functions. A comprehensive understanding of the structure, physiological functions of APP and the interaction between APP and its interacting partners is crucial for the development of novel preventive and therapeutic strategies for AD.

APP is a type I transmembrane protein composed of a large N-terminal luminal region, a single-spanning transmembrane domain and a short C-terminal cytosolic tail [1,2]. Alternative splicing of the *APP* gene generates eight isoforms, with three major isoforms including APP_{695}, APP_{751} and APP_{770} [3]. In the central nervous system, neurons predominantly express the APP_{695} isoform [4]. Two closely related APP-like proteins have been identified in mammals, namely APP-like protein 1 and 2 (APLP1 and APLP2). The N-terminal ectoplasmic domain of APP family proteins (APPs) mainly consisted of E1 and E2 domains, with the acidic domain (AcD) connecting E1 and E2 and the juxtamembrane region (JMR) connecting the ectodomain to the transmembrane helix (TM). In detail, the E1 domain constitutes a growth-factor-like domain (GFLD) and a copper-binding domain (CuBD). E2 domain possesses a heparin-binding domain (HBD) and a CuBD. The Ox-2 antigen domain (Ox-2) and the kunitz protease inhibitor (KPI) domain are also contained in the ectodomain of longer APP isoforms. (Ox-2 in APP_{770}; KPI in APP_{751} and APP_{770}) (Figure 1). The structure of APP resembles cell surface receptors with some putative extracellular ligands [4]. In addition, APP is able to homodimerize or heterodimerize with APLPs and other integral membrane proteins [4]. APP
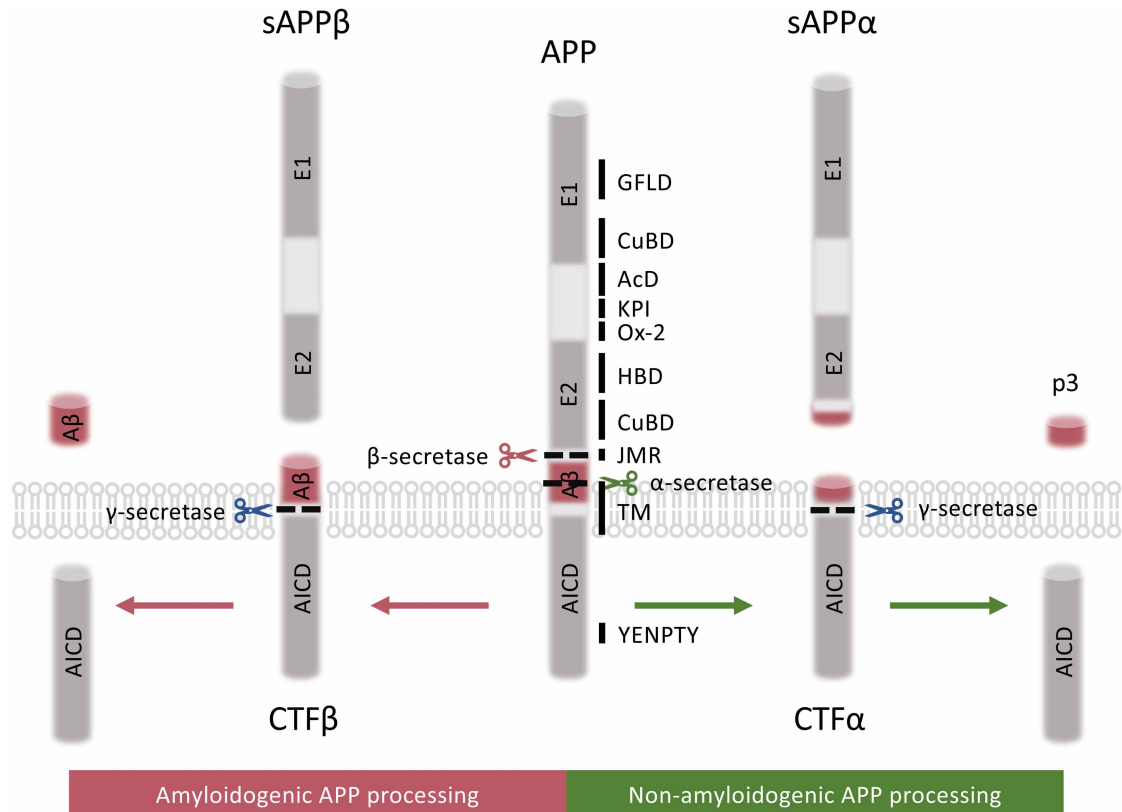
Figure 1. Schematic diagram to show APP structure and processing.

The structure of APP and its non-amyloidogenic and amyloidogenic processing pathways are illustrated. The N-terminal ectoplasmic domain of APP consisted of E1 and E2 domains, with AcD connecting E1 and E2 and JMR connecting the ectodomain to TM. E1 domain constitutes a GFLD and a CuBD. E2 domain possesses a HBD and a CuBD. Ox-2 and KPI domain are also contained in the APP ectodomain. During non-amyloidogenic processing, APP is first cleaved by α-secretase to release sAPPα and membrane-bound CTFα. CTFα is then further cleaved by γ-secretase to produce the p3 fragment and AICD. During amyloidogenic pathway, APP is cleaved by β-secretase to generate sAPPβ and membrane-bound CTFβ, which is further cleaved by γ-secretase to generate Aβ and AICD. 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.

dimerization is dependent on the binding of copper to the HBD and CuBD in APPs [5–7]. On the cytosolic side, the APP intracellular domain (AICD) contains a conserved tyrosine–glutamate–asparagine–proline–threo-nine–tyrosine (YENPTY) motif that is crucial for APP intracellular sorting. Most AICD-interacting proteins contain a phosphotyrosine-binding (PTB) domain, including those in X11/APBA family and FE65/APBB family proteins that recognizes YENPTY motifs [8–10]. Some AICD-interacting proteins have been shown to influence APP processing [11–17].

APP is subjected to regulated intramembrane proteolysis (RIP) which yields secreted extracellular peptides and cytosolic fragments [1]. APP may be metabolized by two mutually exclusive pathways, namely amyloido-genic and non-amyloidogenic pathways (Figure 1). Non-amyloidogenic APP processing by α-secretase and γ-secretase releases secreted APPα (sAPPα) and membrane-bound C-terminal fragment α, which is further cleaved to generate the p3 fragment and AICD [19]. During amyloidogenic processing, stepwise cleavage of APP by β-secretase and γ-secretase produces the neurotoxic Aβ [19]. Under physiological conditions, the

majority of APP is cleaved within the Aβ sequence through the non-amyloidogenic pathway, thus precluding the generation of Aβ. However, a shift towards the amyloidogenic pathway would contribute to an increase in Aβ generation and the pathogenesis in AD. Extracellular deposition of Aβ plaques on neurons is the key pathology hallmark of AD. Both APLP1 and APLP2 undergo RIP via a process similar to that in APP, releasing non-pathological p3-like fragments from APLP1 and p3- and Aβ-like fragments from APLP2 [18].

Despite its pathological role in neurodegeneration, mounting evidence suggests that APPs are crucial for neurodevelopment. APP is first expressed in the developing mouse cortex on embryonic day 9.5, when neurons start to differentiate [19], and its level increases continuously during development [20,21]. The physiological functions of the APPs have been investigated *in vivo* using single-, double- and triple-knockout mouse mutants. Notably, the knockout of only one of the APPs in mice results in subtle phenotypes such as reduced brain weight [22] and muscle weakness [23]. Meanwhile, $App^{-/-}/Aplp2^{-/-}$, $Aplp1^{-/-}/Aplp2^{-/-}$ double knockout and $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$ triple-knockout mouse mutants show early postnatal lethality [24,25]. The triple-knockout mice display major morphological abnormalities with cortical dysplasias, a phenotype that resembles human type II lissencephaly [24]. These studies suggest the functional redundancy of APPs in brain development and postnatal survival [24]. As APPs consist of multiple protein-binding regions and domains, their functions in neurodevelopment are likely contributed, at least in part, by binding to their interactors. Understanding the physical and functional interactions between APP and its interactors is essential for defining their relationship in various signaling pathways and for predicting druggable targets. In this article, we summarize the roles of the interactors that interplay with APP during several major neurodevelopmental events (Figure 2).

The interplay of APP and its interactors during neurodevelopment

Neurogenesis

Neurogenesis is the formation of differentiated neurons from neural precursor cells (NPCs) and the integration of newly formed neurons into the pre-existing neural circuitry. Several findings imply that APP regulates neurogenesis in both developing and adult brains. Ma et al. [26] showed that contactin-2, also known as TAG-1, is a functional APP ligand that suppresses neurogenesis in the developing mouse brain. The effect of APP on neurogenesis has been shown to be associated with the cytosolic adaptor FE65. Abnormalities due to contactin-2 knockout can be reversed by the overexpression of AICD but not an AICD with a mutated FE65 binding site. The binding of contactin-2 to APP stimulates the generation of AICD, which has been shown to complex with FE65 and Tat interactive protein 60 kDa (Tip60) histone acetyltransferase and to modulate gene transactivation [27]. Some AICD-FE65-Tip60-regulated genes including stathmin [28], are implicated in various neuronal processes in adult neurogenesis [29]. Moreover, the AICD–FE65–Tip60 complex participates in neurogenesis through neuronal fate specification and activity-dependent neuroadaptation as Tip60 has been reported to be critical for these two processes [30,31].

The AICD–FE65 complex has also been found to negatively regulate adult neurogenesis, a process associated with hippocampal-mediated memory function [32]. Ghosal et al. [33] showed that adult neurogenesis is impaired in transgenic mice co-expressing AICD and FE65 [33]. Moreover, a synthetic peptide P33 disrupts the APP–FE65 interaction and enhances the memory and learning functions of APPswe/PS1dE9 mice, a common mouse model for studying familial AD, by ameliorating neuroinflammation [34]. Conversely, there are reports suggesting the importance of the APP–FE65 interaction in enhancing or preserving the memory function. The introduction of point mutation threonine 668 (T668) to alanine in APP, which precludes phosphorylation, is shown to prevent memory and synaptic impairments in a familial Danish dementia mouse model [35]. Of note, the phosphorylation of APP residue T668 abolishes the interaction between APP and FE65 [36,37]. Although this discrepancy needs to be resolved, currently available data support the role of the APP–FE65 interaction in adult neurogenesis.

Disabled-1 (Dab1) and disrupted-in-schizophrenia 1 (DISC1) are also AICD interactors implicated in neurogenesis. The stimulatory effect of APP on the migration of cortical neurons is eliminated by a Dab1 binding defective APP mutant. Moreover, overexpression of Dab1 rescues the migration defects caused by APP knockdown in the cortices of the embryos [38]. Likewise, APP knockdown disrupts the localization of DISC1 to the centrosome which results in the faulty migration of embryonic cortical neurons into the cortical plate [39].
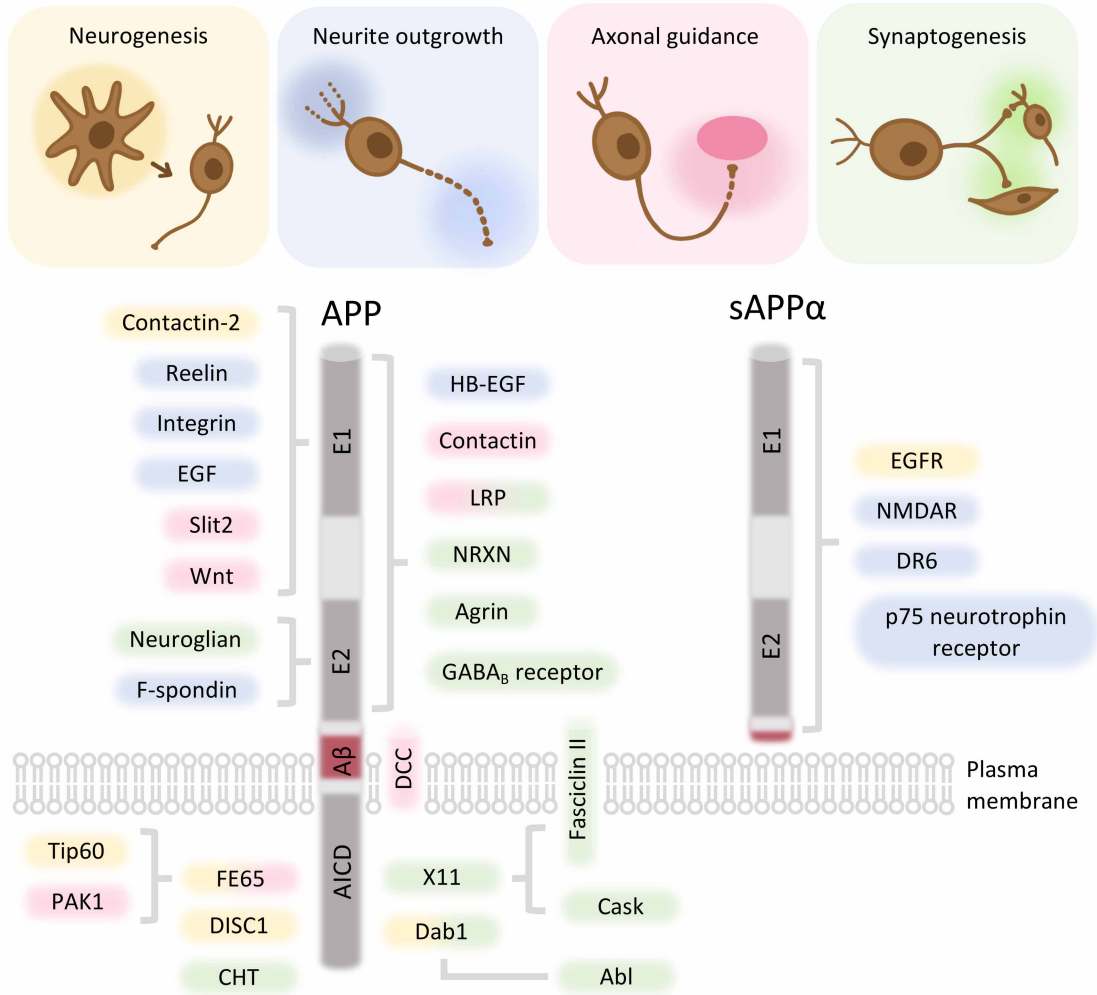
Figure 2. Summary of APP and its interactors in neurodevelopment.

The domains or regions of APP for the binding to its interactors are indicated. The interactors that are associated with APP-mediated neurogenesis (yellow), neurite outgrowth (blue), axonal guidance (pink) and synaptogenesis (green) are shown. APP, amyloid precursor protein; sAPPα, secreted APPα; Aβ, amyloid-β; p3, p3 fragment; E1, E1 domain; E2, E2 domain; AICD, APP intracellular domain; EGF, epidermal growth factor; PAK1, p21-activated kinase 1; DISC1, disrupted-in-schizophrenia 1; HB-EGF, heparin-binding EGF-like growth factor; LRP, low-density lipoprotein receptor-related protein; NRXN, Neurexin; Dab1, Disabled-1; Cask, calcium/calmodulin-dependent serine protein kinase; EGFR, epidermal growth factor receptor; NMDAR, *N*-methyl-D-aspartic acid receptor; DR6, death receptor 6; Abl, Abl tyrosine kinase.

Although it remains unknown how the interactions between APP and Dab1/DISC1 are co-ordinated, the abovementioned findings highlight the significance of APP in cortical migration during development [40].

Intriguingly, overmigration of cortical plate neurons is observed in $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$ triple-knockout mice. The contradictory observation may be due to the difference between acute and chronic genetic depletion models used in different studies. In fact, Young-Pearse et al. [38] observed an increased APLP2 expression in APP knockout but not in APP knockdown animals. Besides, the APPs share several interactors with other type I transmembrane proteins at the Asn-Pro-X-Tyr (NPXY) motif including the members of the low-density lipoprotein receptors (LDLRs) and the Notch receptor family. For instance, APP interacts with reelin, a large secreted extracellular matrix glycoprotein that participates in many neuronal events including neuronal migration [41]. Mutation in the *reelin* gene results in motor dysfunction observed in *reeler* mouse [42]. Malformations of the cortical development have also been observed in the *reeler* mice, which exhibit

inversion of the cortical plate [43]. Of note, $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$ triple-knockout also results in abnormal neuronal positioning. Disorganized and reduced number of Cajal–Retzius (CR) cells is observed in $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$ triple-knockout mice [24]. CR cells are reelin-secreting cells that modulate the architectural development of the cortical plate [44,45]. However, $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$ triple-knockout does not impact the normal inside-out orientation of the cortical layers [24]. Additionally, APP-FE65 interaction is suggested to influence APPs effect on neuronal migration. FE65$^{-/-}$/FE65-like 1 (FE65L1)$^{-/-}$ double knockout mice display focal neuronal ectopia and loss of CR neurons, of which the phenotypes overlap with those observed in $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$ triple-knockout mice [46].

The neurotrophic property of sAPPα has been long observed in multiple cell types. For instance, the addition of sAPPα promotes the proliferation of NPCs while the removal of sAPPα decreases the process. Intraventricular injection of recombinant sAPPα rescues the decline of neurogenesis in the subgranular layer of the dentate gyrus and subventricular zone in ageing mice [47]. As sAPPα co-localizes with NPCs expressing the epidermal growth factor receptor (EGFR), it has been suggested to function as a receptor for sAPPα [48]. Other putative sAPPα receptors have also been proposed. For example, sAPPα interacts with gamma-aminobutyric acid type B receptor (GBR) subunit 1a to modulate neurotransmission [49]. Evidence has shown that GBR signaling mediates hippocampal neurogenesis [50,51]. Moreover, it is suggested that the cell surface APP acts as a sAPPα receptor to the regulate survival of neuroblastoma cells [52]. These findings suggest that sAPPα participates in neurogenesis via multiple signaling pathways.

Neurite outgrowth

Neurite outgrowth is an essential step in nervous system development, as it produces new projections for the wiring of neurons. APP has been shown to regulate neurite outgrowth. Both sAPPα and membrane-associated APP increase the average neurite length [2,53], while APP knockdown inhibits neurite outgrowth [54]. APP is highly expressed in the developing corpus callosum [55], where more than 200 million axons connect the two hemispheres [56]. $App^{-/-}$ and $Aplp2^{-/-}$ knockout mice are shown to have reduced in the density of myelinated axons in corpus callosum region [57]. Moreover, $App^{-/-}$ mice fail to remyelinate after cuprizone-induced demyelination, which was not observed in $Aplp2^{-/-}$ mice, suggesting that APPs regulate myelination differently [57]. In conditional triple APPs knockout mice, loss of all APPs after embryonic day 11.5 results in agenesis of corpus callosum [58]. A mechanism by which APP stimulates neurite outgrowth is via its interaction with reelin, which is known to regulate dendritogenesis [59–61]. The effect of reelin on neurite outgrowth is diminished in APP knockdown neurons [62]. Additionally, integrins, a class of transmembrane proteins that mediate the adhesion of the extracellular matrix and cytoskeleton, are proposed to be involved in APP–reelin-mediated neurite outgrowth as integrin has been shown to interact with these two proteins [62,63]. Indeed, blocking antibodies targeting α3β1 integrin reduces APP- or reelin–mediated dendritic outgrowth in neurons. As reelin has been demonstrated to enhance the interaction between APP and integrin, it has been suggested that the formation of an extracellular tripartite complex of APP, integrin and reelin triggers neurite extension [62].

Another extracellular molecule that may be associated with APP-mediated neurite outgrowth is F-spondin, a secreted morpho-regulatory protein. F-spondin interacts with the E2 domain in the extracellular regions of APP and APLPs via its reelin-like and spondin domains. F-spondin has been shown to promote neurite extension in several types of neurons including dorsal root ganglion (DRG) and commissural neurons [64,65]. Its role in stimulating neurite outgrowth is further supported by the incubation of DRG neurons with anti-F-spondin antibodies which suppresses F-spondin-mediated neurite outgrowth [66]. Conversely, F-spondin exerts an inhibitory effect on the outgrowth of motor axons [65]. These contrasting effects of F-spondin on neurite outgrowth may be due to the existence of different F-spondin interacting partners in different types of neurons. Of note, the protein-binding thrombospondin type 1 repeat 5 (TSR5) and TSR6 domains of F-spondin have been reported to enhance neurite outgrowth, whereas TSR1-4 domains suppress this process [67]. Therefore, it would be interesting to know the effect of F-spondin on neurite outgrowth after complexing with APP or APLPs.

Recently, APP has been reported to stimulate neuritogenesis via the extracellular signal-regulated kinase pathway by interacting with the EGFR ligands epidermal growth factor (EGF) and heparin-binding EGF-like growth factor (HB-EGF). The effects of APP and EGF on neurite outgrowth are abolished by treatment with an EGFR inhibitor [68].

In addition to the holoprotein, soluble APP fragments have also been found to participate in neurite outgrowth [69]. Additionally, sAPP has been found to interact with death receptor 6 (DR6) and trigger the

DR6-dependent degeneration of sensory axons in commissural neurons [70]. Intriguingly, the *cis*-interaction of APP and DR6 has been shown to modulate the axonal pruning of retinal neurons which is a process for remodeling and extension of axons [71]. sAPPα is also required for depolarization-induced neurite outgrowth in neural stem cell-derived neurons through *N*-methyl-D-aspartic acid receptor (NMDAR)- mitogen-activated protein kinase (MAPK) pathway [56]. Of note, NMDAR–MAPK signaling is closely related to neuron survival and synaptic plasticity [72]. Abnormal NMDAR signaling has been implicated in the pathogenesis of AD [73]. As neurite degeneration is commonly observed in AD, it is worth investigating whether aberrant sAPPα/ NMDAR functions contribute to AD pathogenesis.

Axonal guidance

In addition to neurite outgrowth, axonal guidance is an important process in the developing nervous system. During the process, a growing axon is given signal(s) to reach a specific destination. Wang et al. demonstrated that APP, via the E1 domain, mediates axonal guidance through an interaction with Slit2, a member of the Slit family of guidance proteins. Importantly, axon repulsion induced by Slit2 is abolished in a three-dimensional olfactory explant culture derived from $App^{-/-}/Aplp2^{-/-}$ double knockout mice. The downstream effect of Slit2-APP on axonal guidance is thought to be triggered by p21-activated kinase 1 (PAK1) as the neuronal adaptor FE65 mediates the interaction of APP and PAK1. Such APP–FE65–PAK1 complex formation is potentiated by Slit2 [55]. However, it remains unclear how PAK1 is activated in the complex. It is noteworthy that exposure to recombinant Slit2 enhances the activation of Rac1, an upstream activator for PAK1. FE65 also binds to and activates engulfment and cell motility 1 (ELMO1)-dedicator of cytokinesis 1 (DOCK1) bipartite Rac1 guanine nucleotide exchange factor complex [74,75]. It is, therefore, worth investigating the roles of ELMO1–DOCK1 and/or Rac1 in this pathway.

Additionally, APP has been reported to serve as a co-receptor for guidance molecules such as Wnt family proteins which are vital regulators of various developmental processes [76]. For example, APP binds to the canonical Wnt receptor LDLR-related protein 6 (LRP6) to up-regulate the Wnt/β-catenin pathway [77]. Moreover, APP has been demonstrated to complex with DCC, a well-known receptor for the guidance molecule netrin-1, to regulate netrin-1-mediated axonal guidance in commissural neurons [78]. Recently, APP has also been proposed to function as a receptor of Wnt proteins as the cysteine-rich E1 domain of APP has been shown to interact with both Wnt3a and Wnt5a [76]. APP and Wnt3a function to stimulate the growth of axons. Conversely, the effect of Wnt5a on axon growth is promoted in primary neurons with an APP E1 domain deletion mutant which suggests an inhibitory role of Wnt5a-APP in the process [76]. It is possible that APP serves as a universal receptor for the Wnt family proteins to elicit different effects on axonal guidance.

Contactins are brain-enriched proteins belonging to neural immunoglobulin domain-containing cell adhesion molecules (CAMs). APP and APLP have been reported to interact with the contactins through its E1 domain [79–82]. In the developing retinotectal system, contactin-4 regulates the targeting of retinal ganglion cell axons to the nucleus of the optic tract [83]. Intriguingly, ectopic expression of contactin in APP-null mice failed to induce the targeting bias, suggesting that APP is indispensable for this process. Later research has identified that several contactins are able to interact with APPs in a *cis*-orientation, which may function as co-receptors during axon arborization in retinal ganglion cells [82]. It is proposed that APPs-contactins interaction may facilitate the intercellular interaction of another APP-contactin pair or other receptors on the cell surface [82].

Semaphorins (Sema) are diverse extracellular proteins that signals chemorepulsion and growth cone collapse. sAPPα has been shown to bind semaphorin 3A (Sema3A) [84]. Treatment with Sema3A induces growth cone collapse in DRG cells, which is inhibited by the presence of exogenous sAPPα [84]. Notably, the application of synthetic peptides containing the putative sAPPα-interacting sequence of Sema3A blocks the effect of sAPPα [84].

Synaptogenesis

After a growing axon reaches its target, a synapse is required for the presynaptic neuron to transmit a nerve signal to the downstream cells. $App^{-/-}$ knockout mice display an age-dependent decrease in the length and density of dendritic spines [85]. APP-deficient CA1 pyramidal neurons show reduced branching in dendrites [86]. The branching defect is exacerbated in combined $App^{-/-}/Aplp2^{-/-}$ knockout mice [86]. Depletion of APLP1 decreases network inhibition and increases excitatory transmission [87]. In fact, $App^{-/-}/Aplp2^{-/-}$, $Aplp1^{-/-}/Aplp2^{-/-}$ double knockout and $App^{-/-}/Aplp1^{-/-}/Aplp2^{-/-}$ mice die shortly after birth probably due

to severe defects in neuromuscular synapses [24,88,89]. Cell–cell adhesion mediated by CAMs is a crucial step for synaptogenesis. It is believed that APP functions as a CAM in this process because the expression levels of APPs are increased during postembryonic synaptogenesis [90–92]. Moreover, the number of cell contacts are increased in the cells transfected with APPs [5]. Furthermore, excessive axonal terminal sprouting, a characteristic of defective synaptogenesis, is observed in $App^{-/-}/Aplp2^{-/-}$ double knockout mice [88].

In neurons, APP is transported along axons via kinesin-dependent anterograde transport and accumulates in synaptic sites [93,94]. In *Drosophila*, APP-like (APPL) was found to regulate the sorting of the adhesion molecule neuroglian, which has a role in synaptogenesis by organizing cytoskeletal molecules in synaptic terminals [95,96].

Dab1 is another APP interactor implicated in the formation of synapses. Dab1 also binds to Abl tyrosine kinase which is essential for synaptic remodeling [97]. It has been proposed that the effect of APP is triggered through the Dab1–Abl complex as the co-expression of kinase-dead Abl mutant reduces APP-induced axonal arborization [98].

On the other hand, APP is also transported to the postsynaptic terminal via dynein-mediated retrograde transport. In the dendrites, APP may also regulate synaptogenesis by sorting neurotransmitter receptors and CAMs to the synapses. A recent study showed that APP complexes with GBRs to deliver the receptors to the synaptic terminals as defective trafficking of GBRs is observed in $App^{-/-}$ mice [99].

The interaction between APP and neurexins (NRXNs), a family of presynaptic adhesion proteins responsible for the formation and maintenance of synapses, is indispensable for synaptogenesis mediated by APP as the knockdown of NRXNs abolishes this process [100]. It has been proposed that dendritic APP binds and recruits NRXN-β on the axon surface and induces the clustering of NRXNs, which further triggers the recruitment of synaptic vesicles for presynaptic differentiation [100,101].

The mammalian neuromuscular junction (NMJ) is a specialized structure between a motor nerve and a muscle. APP is reported to localize to NMJ [102]. Mice depleted of APP and APLP2 exhibit abnormal NMJ formation and impaired synaptic transmission [88]. The effect of APPs on NMJ function is, at least in part, mediated by the FE65s, as the combined deletion of APLP2 with FE65/FE65L1 exacerbates NMJ deficits when compared with single deletion [103]. Additionally, loss of APP/APLP2 results in the absence of high-affinity choline transporter (CHT) in the presynaptic region. As APP-CTF interacts with CHT, it is proposed that APP functions to regulate the endocytic recycling of the transporter [104].

APP forms a presynaptic complex with X11 and calcium/calmodulin-dependent serine protein kinase (Cask) via AICD, and this complex stimulates presynaptic differentiation [105]. Of note, the X11–Cask complex has been proposed to be a common regulator of synaptic adhesion proteins during presynaptic differentiation through interaction with CAMs [105]. Moreover, in *Drosophila* NMJ, APPL complexes with the CAM fasciclin II to potentiate the effect of the CAM on new synapse formation. It has also been found that neither APPL with the intracellular domain deleted nor *Drosophila* X11 (dX11) with PTB domain deleted stimulates synaptic growth which suggests a role of the APPL–dX11 interaction in this process. It has been suggested fasciclin II, APPL and dX11 form a tripartite complex to transduce fasciclin II signals downstream to trigger synaptogenesis [106].

LRP4, a key regulator of NMJ formation, is another binding partner of APP [107]. In motor neurons, APP, agrin and LRP4 form a hetero-oligomeric complex and cooperatively amplify muscle-specific kinase activation, thereby, inducing the clustering of acetylcholine receptors on the postsynaptic membrane, a hallmark of NMJ formation [107].

Conclusions

Despite of the central pathological roles of aberrant APP processing in neurodegenerative diseases, APPs also play crucial physiological roles in brain development. Many findings, as illustrated here, have demonstrated the significance of the interplay between APP and its interactors in the establishment and maintenance of the nervous system. Additionally, some APP interactors have been found to regulate APP processing which in turn mediates the release of bioactive APP fragments. For example, the interaction between FE65 and APP potentiates APP cleavage while X11 binds APP to suppress the process [11,13–16,108–111]. However, the precise effects of many APP interactors, including autosomal recessive hypercholesterolemia [112,113], on APP processing remain to be determined. Studies on such effects would provide new mechanistic insights into how these APP interactors participate in neurodevelopment by modulating the production of various APP cleavage fragments.

Notably, different APP processing pathways release structurally similar fragments. For instance, both sAPPα and sAPPβ consist of the protein-binding E1 and E2 domains, but they are reported to possess differential biological activities [114–116]. The only difference between the two secreted APPs is the presence of the 16-residues N-terminal Aβ sequence in sAPPα. Whether there is cleavage-specific binding partner(s) or target (s) is needed to be elucidated.

Knockout studies have revealed functional compensation, at least in part, between APPs [22–25]. As they share a similar domain structure, it is expected that the interactors of APP may also bind to APLPs to trigger related physiological responses. However, the unique functions of APPs in the nervous system, such as the differential synaptic roles of APP and APLPs in NMJ synapses, have also been reported [117]. The differential functions of APPs may be contributed by their recruitment of different interactors or differences in binding affinity toward the same interactor. Thus, detailed comparative studies of the interactions of APPs and their interactors are needed.

Differential expression of APP in various developmental stages and regions of the brain has been shown [19–21,92,118,119]. Likewise, the expression of APP interactors has also been found altered during development [120–122]. Of note, competition between interactors that bind to APP through the same region or domain is observed. For instance, FE65 and X11 compete for the binding of the AICD [123]. Although it remains unknown, the spatial-temporal expression and regulation of APP interactors at different neurodevelopmental phases may play a significant role in coordinating their interactions with APP. Moreover, our knowledge of how the differential binding of APP interactors is controlled remains limited. It is noteworthy that APP and some of its interactors are phosphoproteins. Many findings have revealed the crucial roles of protein phosphorylation in various neuronal processes [124]. Several reports have shown the importance of phosphorylation in modulating the bindings between APP and its interactors [14,36,125,126]. Further studies on the mechanisms that regulate APP interactions, including phosphorylation-dependent interactome analysis, would provide more mechanistic insights into how APP interplays with different interactors.

Although many APP interactors have been demonstrated to participate in different neuronal processes, such as FE65 in neurite outgrowth [74,75,127,128], their effects after binding to APPs remain elusive. Elucidation of the roles of these APP–interactor complexes would provide further insights into how these interactors participate in APP-mediated neurodevelopmental processes.

The generation of Aβ is a major focus in the study of the pathological roles of APP. However, evidence also suggests alternative pathological roles of APP. For instance, the D678N mutation on APP has been reported to cause AD-related dementia without a significant change in Aβ production [129] which suggests the impairment of other APP-associated processes. Notably, many neurodevelopmental processes that involve APP, including neurogenesis [130], neurite outgrowth [98,131] and synaptogenesis [132], are conserved in the adult nervous system. Defects in these neurodevelopmental processes have been observed in various neurodegenerative disorders such as AD and Parkinson's disease [133,134]. Targeting these processes that are mediated by APP–interactor complexes may be a novel avenue for the treatment of these disorders. Future investigations of the physiological roles of APP and its interactors would lead to a better understanding of their relationships with neurodegenerative diseases and would provide important information to facilitate the development of effective therapeutic interventions for these diseases.

Perspectives

- There has been significant progress toward understanding the physiological roles of APP and its interactors in the development of the nervous system.

- The APP interactome has been implicated in modulating the diverse biological activities of APP. Identification of novel APP interactors is fundamental to increase our knowledge of the APP-regulated signaling.

- The linkage between APP physiological and pathological roles remains unclear. Elucidating how APP interactions contribute to normal neuronal functions offers insights into how APP may directly contribute to the pathogenesis of several neurological diseases.

PORTLAND
PRESS

Competing Interests

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

Funding

Open Access

Open access for this article was enabled by the participation of Chinese University of Hong Kong in an all-inclusive *Read & Publish* agreement with Portland Press and the Biochemical Society under a transformative agreement with JULAC.

Author Contributions

D.D.-L.C., L.L.-H.N., Y.Z. and K.-F.L. wrote the manuscript.

Abbreviations

AcD, acidic domain; AD, Alzheimer's disease; AICD, APP intracellular domain; APLP, APP-like protein; APP, amyloid precursor protein; APPL, APP-like; APPs, APP family proteins; Aβ, amyloid-β; CAM, cell adhesion molecule; Cask, calcium/calmodulin-dependent serine protein kinase; CHT, high-affinity choline transporter; CR, Cajal–Retzius; CTF, C-terminal fragment; CuBD, copper-binding domain; Dab1, Disabled-1; DISC1, disrupted-in-schizophrenia 1; DOCK1, dedicator of cytokinesis 1; DR6, death receptor 6; DRG, dorsal root ganglion; dX11, *Drosophila* X11; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ELMO1, engulfment and cell motility 1; GBR, gamma-aminobutyric acid type B receptors; GEF, guanine nucleotide exchange factor; GFLD, growth-factor-like domain; HBD, heparin-binding domain; HB-EGF, heparin-binding EGF-like growth factor; JMR, juxtamembrane region; KPI, kunitz protease inhibitor; LDLRs, low-density lipoprotein receptors; LRP, low-density lipoprotein receptor-related protein; NMDAR, *N*-methyl-D-aspartic acid receptor; NMJ, neuromuscular junction; NPCs, neural precursor cells; NRXN, neurexin; Ox-2, Ox-2 antigen domain; PAK1, p21-activated kinase 1; PTB, phosphotyrosine-binding; RIP, regulated intramembrane proteolysis; sAPP, secreted APP; Sema, Semaphorins; T668, threonine 668; Tip60, Tat interactive protein 60kDa; TSR, thrombospondin type 1 repeat; YENPTY, tyrosine–glutamate–asparagine–proline–threonine–tyrosine; ZnBD, zinc-binding domain.

References

1 Jacobsen, K.T. and Iverfeldt, K. (2009) Amyloid precursor protein and its homologues: a family of proteolysis-dependent receptors. *Cell. Mol. Life Sci.* **66**, 2299–2318 https://doi.org/10.1007/s00018-009-0020-8
2 Gralle, M. and Ferreira, S.T. (2007) Structure and functions of the human amyloid precursor protein: the whole is more than the sum of its parts. *Prog. Neurobiol.* **82**, 11–32 https://doi.org/10.1016/j.pneurobio.2007.02.001
3 Sandbrink, R., Masters, C.L. and Beyreuther, K. (1996) APP gene family. Alternative splicing generates functionally related isoforms. *Ann. NY Acad. Sci.* **777**, 281–287 https://doi.org/10.1111/j.1749-6632.1996.tb34433.x
4 Kang, J., Lemaire, H.G., Unterbeck, A., Salbaum, J.M., Masters, C.L., Grzeschik, K.H. et al. (1987) The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature* **325**, 733–736 https://doi.org/10.1038/325733a0
5 Soba, P., Eggert, S., Wagner, K., Zentgraf, H., Siehl, K., Kreger, S. et al. (2005) Homo- and heterodimerization of APP family members promotes intercellular adhesion. *EMBO J.* **24**, 3624–3634 https://doi.org/10.1038/sj.emboj.7600824
6 Dahms, S.O., Hoefgen, S., Roeser, D., Schlott, B., Guhrs, K.H. and Than, M.E. (2010) Structure and biochemical analysis of the heparin-induced E1 dimer of the amyloid precursor protein. *Proc. Natl Acad. Sci. U.S.A.* **107**, 5381–5386 https://doi.org/10.1073/pnas.0911326107
7 Baumkotter, F., Schmidt, N., Vargas, C., Schilling, S., Weber, R., Wagner, K. et al. (2014) Amyloid precursor protein dimerization and synaptogenic function depend on copper binding to the growth factor-like domain. *J. Neurosci.* **34**, 11159–11172 https://doi.org/10.1523/JNEUROSCI.0180-14.2014
8 Yan, K.S., Kuti, M. and Zhou, M.M. (2002) PTB or not PTB – that is the question. *FEBS Lett.* **513**, 67–70 https://doi.org/10.1016/S0014-5793(01)03305-1
9 Rogelj, B., Mitchell, J.C., Miller, C.C. and McLoughlin, D.M. (2006) The X11/Mint family of adaptor proteins. *Brain Res. Rev.* **52**, 305–315 https://doi.org/10.1016/j.brainresrev.2006.04.005
10 McLoughlin, D.M. and Miller, C.C. (2008) The FE65 proteins and Alzheimer's disease. *J. Neurosci. Res.* **86**, 744–754 https://doi.org/10.1002/jnr.21532
11 Sabo, S.L., Lanier, L.M., Ikin, A.F., Khorkova, O., Sahasrabudhe, S., Greengard, P. et al. (1999) Regulation of beta-amyloid secretion by FE65, an amyloid protein precursor-binding protein. *J. Biol. Chem.* **274**, 7952–7957 https://doi.org/10.1074/jbc.274.12.7952
12 Ando, K., Iijima, K.I., Elliott, J.I., Kirino, Y. and Suzuki, T. (2001) Phosphorylation-dependent regulation of the interaction of amyloid precursor protein with Fe65 affects the production of beta-amyloid. *J. Biol. Chem.* **276**, 40353–40361 https://doi.org/10.1074/jbc.M104059200

13   Chow, W.N., Ngo, J.C., Li, W., Chen, Y.W., Tam, K.M., Chan, H.E. et al. (2015) Phosphorylation of FE65 Serine-610 by serum- and glucocorticoid-induced kinase 1 modulates Alzheimer's disease amyloid precursor protein processing. *Biochem. J.* **470**, 303–317 https://doi.org/10.1042/BJ20141485

14   Lee, Y.S., Chow, W.N.V. and Lau, K.F. (2017) Phosphorylation of FE65 at threonine 579 by GSK3beta stimulates amyloid precursor protein processing. *Sci. Rep.* **7**, 12456 https://doi.org/10.1038/s41598-017-12334-2

15   Lee, J.H., Lau, K.F., Perkinton, M.S., Standen, C.L., Rogelj, B., Falinska, A. et al. (2004) The neuronal adaptor protein X11b reduces amyloid b-protein levels and amyloid plaque formation in the brains of transgenic mice. *J. Biol. Chem.* **279**, 49099–49104 https://doi.org/10.1074/jbc.M405602200

16   Sano, Y., Syuzo-Takabatake, A., Nakaya, T., Saito, Y., Tomita, S., Itohara, S. et al. (2006) Enhanced amyloidogenic metabolism of APP in the X11L-deficient mouse brain. *J. Biol. Chem.* **281**, 37853–37860 https://doi.org/10.1074/jbc.M609312200

17   Saluja, I., Paulson, H., Gupta, A. and Turner, R.S. (2009) X11alpha haploinsufficiency enhances Abeta amyloid deposition in Alzheimer's disease transgenic mice. *Neurobiol. Dis.* **36**, 162–168 https://doi.org/10.1016/j.nbd.2009.07.006

18   Eggert, S., Paliga, K., Soba, P., Evin, G., Masters, C.L., Weidemann, A. et al. (2004) The proteolytic processing of the amyloid precursor protein gene family members APLP-1 and APLP-2 involves alpha-, beta-, gamma-, and epsilon-like cleavages: modulation of APLP-1 processing by n-glycosylation. *J. Biol. Chem.* **279**, 18146–18156 https://doi.org/10.1074/jbc.M311601200

19   Salbaum, J.M. and Ruddle, F.H. (1994) Embryonic expression pattern of amyloid protein precursor suggests a role in differentiation of specific subsets of neurons. *J. Exp. Zool.* **269**, 116–127 https://doi.org/10.1002/jez.1402690205

20   Arai, H., Higuchi, S., Matsushita, S., Yuzuriha, T., Trojanowski, J.Q. and Lee, V.M. (1994) Expression of beta-amyloid precursor protein in the developing human spinal cord. *Brain Res.* **642**, 132–136 https://doi.org/10.1016/0006-8993(94)90914-8

21   Ohta, M., Kitamoto, T., Iwaki, T., Ohgami, T., Fukui, M. and Tateishi, J. (1993) Immunohistochemical distribution of amyloid precursor protein during normal rat development. *Brain Res. Dev. Brain Res.* **75**, 151–161 https://doi.org/10.1016/0165-3806(93)90019-7

22   Magara, F., Muller, U., Li, Z.W., Lipp, H.P., Weissmann, C., Stagljar, M. et al. (1999) Genetic background changes the pattern of forebrain commissure defects in transgenic mice underexpressing the beta-amyloid-precursor protein. *Proc. Natl Acad. Sci. U.S.A.* **96**, 4656–4661 https://doi.org/10.1073/pnas.96.8.4656

23   Zheng, H., Jiang, M., Trumbauer, M.E., Sirinathsinghji, D.J., Hopkins, R., Smith, D.W. et al. (1995) beta-Amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity. *Cell* **81**, 525–531 https://doi.org/10.1016/0092-8674(95)90073-x

24   Herms, J., Anliker, B., Heber, S., Ring, S., Fuhrmann, M., Kretzschmar, H. et al. (2004) Cortical dysplasia resembling human type 2 lissencephaly in mice lacking all three APP family members. *EMBO J.* **23**, 4106–4115 https://doi.org/10.1038/sj.emboj.7600390

25   Heber, S., Herms, J., Gajic, V., Hainfellner, J., Aguzzi, A., Rulicke, T. et al. (2000) Mice with combined gene knock-outs reveal essential and partially redundant functions of amyloid precursor protein family members. *J. Neurosci.* **20**, 7951–7963 https://doi.org/10.1523/JNEUROSCI.20-21-07951.2000

26   Ma, Q.H., Futagawa, T., Yang, W.L., Jiang, X.D., Zeng, L., Takeda, Y. et al. (2008) A TAG1-APP signalling pathway through Fe65 negatively modulates neurogenesis. *Nat. Cell Biol.* **10**, 283–294 https://doi.org/10.1038/ncb1690

27   Probst, S., Kruger, M., Kagi, L., Thoni, S., Schuppli, D., Nitsch, R.M. et al. (2020) Fe65 is the sole member of its family that mediates transcription regulated by the amyloid precursor protein. *J. Cell Sci.* **133**. https://doi.org/10.1242/jcs.242917

28   Muller, T., Schrotter, A., Loosse, C., Pfeiffer, K., Theiss, C., Kauth, M. et al. (2013) A ternary complex consisting of AICD, FE65, and TIP60 down-regulates Stathmin1. *Biochim. Biophys. Acta* **1834**, 387–394 https://doi.org/10.1016/j.bbapap.2012.07.017

29   Jin, K., Mao, X.O., Cottrell, B., Schilling, B., Xie, L., Row, R.H. et al. (2004) Proteomic and immunochemical characterization of a role for stathmin in adult neurogenesis. *FASEB J.* **18**, 287–299 https://doi.org/10.1096/fj.03-0973com

30   Janas, J.A., Zhang, L., Luu, J.H., Demeter, J., Meng, L., Marro, S.G. et al. (2022) Tip60-mediated H2A.Z acetylation promotes neuronal fate specification and bivalent gene activation. *Mol. Cell* **82**, 4627–46.e14 https://doi.org/10.1016/j.molcel.2022.11.002

31   Pirooznia, S.K., Sarthi, J., Johnson, A.A., Toth, M.S., Chiu, K., Koduri, S. et al. (2012) Tip60 HAT activity mediates APP induced lethality and apoptotic cell death in the CNS of a Drosophila Alzheimer's disease model. *PLoS One* **7**, e41776 https://doi.org/10.1371/journal.pone.0041776

32   Deng, W., Aimone, J.B. and Gage, F.H. (2010) New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat. Rev. Neurosci.* **11**, 339–350 https://doi.org/10.1038/nrn2822

33   Ghosal, K., Stathopoulos, A. and Pimplikar, S.W. (2010) APP intracellular domain impairs adult neurogenesis in transgenic mice by inducing neuroinflammation. *PLoS One* **5**, e11866 https://doi.org/10.1371/journal.pone.0011866

34   Szogi, T., Schuster, I., Borbely, E., Gyebrovszki, A., Bozso, Z., Gera, J. et al. (2019) Effects of the pentapeptide P33 on memory and synaptic plasticity in APP/PS1 transgenic mice: a novel mechanism presenting the protein Fe65 as a target. *Int. J. Mol. Sci.* **20**. https://doi.org/10.3390/ijms20123050

35   Lombino, F., Biundo, F., Tamayev, R., Arancio, O. and D'Adamio, L. (2013) An intracellular threonine of amyloid-beta precursor protein mediates synaptic plasticity deficits and memory loss. *PLoS One* **8**, e57120 https://doi.org/10.1371/journal.pone.0057120

36   Chang, K.A., Kim, H.S., Ha, T.Y., Ha, J.W., Shin, K.Y., Jeong, Y.H. et al. (2006) Phosphorylation of amyloid precursor protein (APP) at Thr668 regulates the nuclear translocation of the APP intracellular domain and induces neurodegeneration. *Mol. Cell. Biol.* **26**, 4327–4338 https://doi.org/10.1128/MCB.02393-05

37   Lee, M.S., Kao, S.C., Lemere, C.A., Xia, W., Tseng, H.C., Zhou, Y. et al. (2003) APP processing is regulated by cytoplasmic phosphorylation. *J. Cell Biol.* **163**, 83–95 https://doi.org/10.1083/jcb.200301115

38   Young-Pearse, T.L., Bai, J., Chang, R., Zheng, J.B., LoTurco, J.J. and Selkoe, D.J. (2007) A critical function for beta-amyloid precursor protein in neuronal migration revealed by in utero RNA interference. *J. Neurosci.* **27**, 14459–14469 https://doi.org/10.1523/JNEUROSCI.4701-07.2007

39   Young-Pearse, T.L., Suth, S., Luth, E.S., Sawa, A. and Selkoe, D.J. (2010) Biochemical and functional interaction of disrupted-in-schizophrenia 1 and amyloid precursor protein regulates neuronal migration during mammalian cortical development. *J. Neurosci.* **30**, 10431–10440 https://doi.org/10.1523/JNEUROSCI.1445-10.2010

40   Chen, L., Zhu, L., Xu, J., Xu, P., Han, Y., Chang, L. et al. (2022) Disrupted in schizophrenia 1 regulates ectopic neurogenesis in the mouse hilus after pilocarpine-induced status epilepticus. *Neuroscience* **494**, 69–81 https://doi.org/10.1016/j.neuroscience.2022.05.009

41   Lee, G.H. and D'Arcangelo, G. (2016) New insights into reelin-mediated signaling pathways. *Front. Cell. Neurosci.* **10**, 122 https://doi.org/10.3389/fncel.2016.00122

42   Bar, I., De Rouvroit C, L., Royaux, I., Krizman, D.B., Dernoncourt, C., Ruelle, D. et al. (1995) A YAC contig containing the reeler locus with preliminary characterization of candidate gene fragments. *Genomics* **26**, 543–549 https://doi.org/10.1016/0888-7543(95)80173-j

43 Caviness VS, J. and Sidman, R.L. (1973) Time of origin or corresponding cell classes in the cerebral cortex of normal and reeler mutant mice: an autoradiographic analysis. *J. Comp. Neurol.* **148**, 141–151 https://doi.org/10.1002/cne.901480202

44 Hartmann, D., De Strooper, B. and Saftig, P. (1999) Presenilin-1 deficiency leads to loss of Cajal-Retzius neurons and cortical dysplasia similar to human type 2 lissencephaly. *Curr. Biol.* **9**, 719–727 https://doi.org/10.1016/s0960-9822(99)80331-5

45 Hirota, Y. and Nakajima, K. (2017) Control of neuronal migration and aggregation by reelin signaling in the developing cerebral cortex. *Front. Cell Dev. Biol.* **5**, 40 https://doi.org/10.3389/fcell.2017.00040

46 Guenette, S., Chang, Y., Hiesberger, T., Richardson, J.A., Eckman, C.B., Eckman, E.A. et al. (2006) Essential roles for the FE65 amyloid precursor protein-interacting proteins in brain development. *EMBO J.* **25**, 420–431 https://doi.org/10.1038/sj.emboj.7600926

47 Demars, M.P., Hollands, C., Zhao Kda, T. and Lazarov, O. (2013) Soluble amyloid precursor protein-alpha rescues age-linked decline in neural progenitor cell proliferation. *Neurobiol. Aging* **34**, 2431–2440 https://doi.org/10.1016/j.neurobiolaging.2013.04.016

48 Caille, I., Allinquant, B., Dupont, E., Bouillot, C., Langer, A., Muller, U. et al. (2004) Soluble form of amyloid precursor protein regulates proliferation of progenitors in the adult subventricular zone. *Development* **131**, 2173–2181 https://doi.org/10.1242/dev.01103

49 Rice, H.C., de Malmazet, D., Schreurs, A., Frere, S., Van Molle, I., Volkov, A.N. et al. (2019) Secreted amyloid-beta precursor protein functions as a GABA(B)R1a ligand to modulate synaptic transmission. *Science* **363**. https://doi.org/10.1126/science.aao4827

50 Giachino, C., Barz, M., Tchorz, J.S., Tome, M., Gassmann, M., Bischofberger, J. et al. (2014) GABA suppresses neurogenesis in the adult hippocampus through GABAB receptors. *Development* **141**, 83–90 https://doi.org/10.1242/dev.102608

51 Gustorff, C., Scheuer, T., Schmitz, T., Buhrer, C. and Endesfelder, S. (2021) GABA(b) receptor-mediated impairment of intermediate progenitor maturation during postnatal hippocampal neurogenesis of newborn rats. *Front. Cell. Neurosci.* **15**, 651072 https://doi.org/10.3389/fncel.2021.651072

52 Gralle, M., Botelho, M.G. and Wouters, F.S. (2009) Neuroprotective secreted amyloid precursor protein acts by disrupting amyloid precursor protein dimers. *J. Biol. Chem.* **284**, 15016–15025 https://doi.org/10.1074/jbc.M808755200

53 Milward, E.A., Papadopoulos, R., Fuller, S.J., Moir, R.D., Small, D., Beyreuther, K. et al. (1992) The amyloid protein precursor of Alzheimer's disease is a mediator of the effects of nerve growth factor on neurite outgrowth. *Neuron* **9**, 129–137 https://doi.org/10.1016/0896-6273(92)90228-6

54 Allinquant, B., Hantraye, P., Mailleux, P., Moya, K., Bouillot, C. and Prochiantz, A. (1995) Downregulation of amyloid precursor protein inhibits neurite outgrowth in vitro. *J. Cell Biol.* **128**, 919–927 https://doi.org/10.1083/jcb.128.5.919

55 Wang, B., Li, H., Mutlu, S.A., Bowser, D.A., Moore, M.J., Wang, M.C. et al. (2017) The amyloid precursor protein is a conserved receptor for slit to mediate axon guidance. *eNeuro* **4**. https://doi.org/10.1523/ENEURO.0185-17.2017

56 Funnell, M.G., Corballis, P.M. and Gazzaniga, M.S. (2000) Cortical and subcortical interhemispheric interactions following partial and complete callosotomy. *Arch. Neurol.* **57**, 185–189 https://doi.org/10.1001/archneur.57.2.185

57 Truong, P.H., Ciccotosto, G.D., Merson, T.D., Spoerri, L., Chuei, M.J., Ayers, M. et al. (2019) Amyloid precursor protein and amyloid precursor-like protein 2 have distinct roles in modulating myelination, demyelination, and remyelination of axons. *Glia* **67**, 525–538 https://doi.org/10.1002/glia.23561

58 Steubler, V., Erdinger, S., Back, M.K., Ludewig, S., Fassler, D., Richter, M. et al. (2021) Loss of all three APP family members during development impairs synaptic function and plasticity, disrupts learning, and causes an autism-like phenotype. *EMBO J.* **40**, e107471 https://doi.org/10.15252/embj.2020107471

59 Trommsdorff, M., Gotthardt, M., Hiesberger, T., Shelton, J., Stockinger, W., Nimpf, J. et al. (1999) Reeler/disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. *Cell* **97**, 689–701 https://doi.org/10.1016/s0092-8674(00)80782-5

60 Niu, S., Yabut, O. and D'Arcangelo, G. (2008) The reelin signaling pathway promotes dendritic spine development in hippocampal neurons. *J. Neurosci.* **28**, 10339–10348 https://doi.org/10.1523/JNEUROSCI.1917-08.2008

61 Bu, G. (2009) Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat. Rev. Neurosci.* **10**, 333–344 https://doi.org/10.1038/nrn2620

62 Hoe, H.S., Lee, K.J., Carney, R.S., Lee, J., Markova, A., Lee, J.Y. et al. (2009) Interaction of reelin with amyloid precursor protein promotes neurite outgrowth. *J. Neurosci.* **29**, 7459–7473 https://doi.org/10.1523/JNEUROSCI.4872-08.2009

63 Schmid, R.S., Jo, R., Shelton, S., Kreidberg, J.A. and Reelin, A.E. (2005) Integrin and DAB1 interactions during embryonic cerebral cortical development. *Cereb Cortex* **15**, 1632–1636 https://doi.org/10.1093/cercor/bhi041

64 Klar, A., Baldassare, M. and Jessell, T.M. (1992) F-spondin: a gene expressed at high levels in the floor plate encodes a secreted protein that promotes neural cell adhesion and neurite extension. *Cell* **69**, 95–110 https://doi.org/10.1016/0092-8674(92)90121-r

65 Tzarfati-Majar, V., Burstyn-Cohen, T. and Klar, A. (2001) F-spondin is a contact-repellent molecule for embryonic motor neurons. *Proc. Natl Acad. Sci. U.S.A.* **98**, 4722–4727 https://doi.org/10.1073/pnas.081062398

66 Burstyn-Cohen, T., Frumkin, A., Xu, Y.T., Scherer, S.S. and Klar, A. (1998) Accumulation of F-spondin in injured peripheral nerve promotes the outgrowth of sensory axons. *J. Neurosci.* **18**, 8875–8885 https://doi.org/10.1523/JNEUROSCI.18-21-08875.1998

67 Zisman, S., Marom, K., Avraham, O., Rinsky-Halivni, L., Gai, U., Kligun, G. et al. (2007) Proteolysis and membrane capture of F-spondin generates combinatorial guidance cues from a single molecule. *J. Cell Biol.* **178**, 1237–1249 https://doi.org/10.1083/jcb.200702184

68 da Rocha, J.F., Bastos, L., Domingues, C. and Bento, A.R. (2021) Konietzko U, da Cruz ESOAB, et al. APP binds to the EGFR ligands HB-EGF and EGF, acting synergistically with EGF to promote ERK signaling and neuritogenesis. *Mol. Neurobiol.* **58**, 668–688 https://doi.org/10.1007/s12035-020-02139-2

69 Hasebe, N., Fujita, Y., Ueno, M., Yoshimura, K., Fujino, Y. and Yamashita, T. (2013) Soluble beta-amyloid precursor protein alpha binds to p75 neurotrophin receptor to promote neurite outgrowth. *PLoS One* **8**, e82321 https://doi.org/10.1371/journal.pone.0082321

70 Nikolaev, A., McLaughlin, T., O'Leary, D.D. and Tessier-Lavigne, M. (2009) APP binds DR6 to trigger axon pruning and neuron death via distinct caspases. *Nature* **457**, 981–99 https://doi.org/10.1038/nature07767

71 Olsen, O., Kallop, D.Y., McLaughlin, T., Huntwork-Rodriguez, S., Wu, Z., Duggan, C.D. et al. (2014) Genetic analysis reveals that amyloid precursor protein and death receptor 6 function in the same pathway to control axonal pruning independent of beta-secretase. *J. Neurosci.* **34**, 6438–6447 https://doi.org/10.1523/JNEUROSCI.3522-13.2014

72 Impey, S., Obrietan, K. and Storm, D.R. (1999) Making new connections: role of ERK/MAP kinase signaling in neuronal plasticity. *Neuron* **23**, 11–14 https://doi.org/10.1016/s0896-6273(00)80747-3

73 Wang, R. and Reddy, P.H. (2017) Role of glutamate and NMDA receptors in Alzheimer's disease. *J. Alzheimer's Dis.* **57**, 1041–1048 https://doi.org/10.3233/JAD-160763

74 Li, W., Tam, K.M.V., Chan, W.W.R., Koon, A.C., Ngo, J.C.K., Chan, H.Y.E. et al. (2018) Neuronal adaptor FE65 stimulates Rac1-mediated neurite outgrowth by recruiting and activating ELMO1. *J. Biol. Chem.* **293**, 7674–7688 https://doi.org/10.1074/jbc.RA117.000505

75 Chan, W.W.R., Li, W., Chang, R.C.C. and Lau, K.F. (2020) ARF6-Rac1 signaling-mediated neurite outgrowth is potentiated by the neuronal adaptor FE65 through orchestrating ARF6 and ELMO1. *FASEB J.* **34**, 16397–16413 https://doi.org/10.1096/fj.202001703R

76 Liu, T., Zhang, T., Nicolas, M., Boussicault, L., Rice, H., Soldano, A. et al. (2021) The amyloid precursor protein is a conserved Wnt receptor. *eLife* **10**. https://doi.org/10.7554/eLife.69199

77 Elliott, C., Rojo, A.I., Ribe, E., Broadstock, M., Xia, W., Morin, P. et al. (2018) A role for APP in Wnt signalling links synapse loss with beta-amyloid production. *Transl. Psychiatry* **8**, 179 https://doi.org/10.1038/s41398-018-0231-6

78 Rama, N., Goldschneider, D., Corset, V., Lambert, J., Pays, L. and Mehlen, P. (2012) Amyloid precursor protein regulates netrin-1-mediated commissural axon outgrowth. *J. Biol. Chem.* **287**, 30014–30023 https://doi.org/10.1074/jbc.M111.324780

79 Osterfield, M., Egelund, R., Young, L.M. and Flanagan, J.G. (2008) Interaction of amyloid precursor protein with contactins and NgCAM in the retinotectal system. *Development* **135**, 1189–1199 https://doi.org/10.1242/dev.007401

80 Bamford, R.A., Widagdo, J., Takamura, N., Eve, M., Anggono, V. and Oguro-Ando, A. (2020) The interaction between contactin and amyloid precursor protein and its role in Alzheimer's disease. *Neuroscience* **424**, 184–202 https://doi.org/10.1016/j.neuroscience.2019.10.006

81 Peng, X., Williams, J., Smallwood, P.M. and Nathans, J. (2019) Defining the binding interface of amyloid precursor protein (APP) and contactin3 (CNTN3) by site-directed mutagenesis. *PLoS One* **14**, e0219384 https://doi.org/10.1371/journal.pone.0219384

82 Karuppan, S.J., Vogt, A., Fischer, Z., Ladutska, A., Swiastyn, J., McGraw, H.F. et al. (2022) Members of the vertebrate contactin and amyloid precursor protein families interact through a conserved interface. *J. Biol. Chem.* **298**, 101541 https://doi.org/10.1016/j.jbc.2021.101541

83 Osterhout, J.A., Stafford, B.K., Nguyen, P.L., Yoshihara, Y. and Huberman, A.D. (2015) Contactin-4 mediates axon-target specificity and functional development of the accessory optic system. *Neuron* **86**, 985–999 https://doi.org/10.1016/j.neuron.2015.04.005

84 Magdesian, M.H., Gralle, M., Guerreiro, L.H., Beltrao, P.J., Carvalho, M.M., Santos, L.E. et al. (2011) Secreted human amyloid precursor protein binds semaphorin 3a and prevents semaphorin-induced growth cone collapse. *PLoS One* **6**, e22857 https://doi.org/10.1371/journal.pone.0022857

85 Lee, K.J., Moussa, C.E., Lee, Y., Sung, Y., Howell, B.W., Turner, R.S. et al. (2010) Beta amyloid-independent role of amyloid precursor protein in generation and maintenance of dendritic spines. *Neuroscience* **169**, 344–356 https://doi.org/10.1016/j.neuroscience.2010.04.078

86 Weyer, S.W., Zagrebelsky, M., Herrmann, U., Hick, M., Ganss, L., Gobbert, J. et al. (2014) Comparative analysis of single and combined APP/APLP knockouts reveals reduced spine density in APP-KO mice that is prevented by APPsalpha expression. *Acta Neuropathol. Commun.* **2**, 36 https://doi.org/10.1186/2051-5960-2-36

87 Vnencak, M., Paul, M.H., Hick, M., Schwarzacher, S.W., Del Turco, D., Muller, U.C. et al. (2015) Deletion of the amyloid precursor-like protein 1 (APLP1) enhances excitatory synaptic transmission, reduces network inhibition but does not impair synaptic plasticity in the mouse dentate gyrus. *J. Comp. Neurol.* **523**, 1717–1729 https://doi.org/10.1002/cne.23766

88 Wang, P., Yang, G., Mosier, D.R., Chang, P., Zaidi, T., Gong, Y.D. et al. (2005) Defective neuromuscular synapses in mice lacking amyloid precursor protein (APP) and APP-like protein 2. *J. Neurosci.* **25**, 1219–1225 https://doi.org/10.1523/JNEUROSCI.4660-04.2005

89 von Koch, C.S., Zheng, H., Chen, H., Trumbauer, M., Thinakaran, G., van der Ploeg, L.H. et al. (1997) Generation of APLP2 KO mice and early postnatal lethality in APLP2/APP double KO mice. *Neurobiol. Aging* **18**, 661–669 https://doi.org/10.1016/s0197-4580(97)00151-6

90 Moya, K.L., Benowitz, L.I., Schneider, G.E. and Allinquant, B. (1994) The amyloid precursor protein is developmentally regulated and correlated with synaptogenesis. *Dev. Biol.* **161**, 597–603 https://doi.org/10.1006/dbio.1994.1055

91 Sandbrink, R., Masters, C.L. and Beyreuther, K. (1994) Similar alternative splicing of a non-homologous domain in beta A4-amyloid protein precursor-like proteins. *J. Biol. Chem.* **269**, 14227–14234 https://doi.org/10.1016/S0021-9258(17)36778-9

92 Lorent, K., Overbergh, L., Moechars, D., De Strooper, B., Van Leuven, F. and Van den Berghe, H. (1995) Expression in mouse embryos and in adult mouse brain of three members of the amyloid precursor protein family, of the alpha-2-macroglobulin receptor/low density lipoprotein receptor-related protein and of its ligands apolipoprotein E, lipoprotein lipase, alpha-2-macroglobulin and the 40,000 molecular weight receptor-associated protein. *Neuroscience* **65**, 1009–1025 https://doi.org/10.1016/0306-4522(94)00555-j

93 Koo, E.H., Sisodia, S.S., Archer, D.R., Martin, L.J., Weidemann, A., Beyreuther, K. et al. (1990) Precursor of amyloid protein in Alzheimer disease undergoes fast anterograde axonal transport. *Proc. Natl Acad. Sci. U.S.A.* **87**, 1561–1565 https://doi.org/10.1073/pnas.87.4.1561

94 Buxbaum, J.D., Thinakaran, G., Koliatsos, V., O'Callahan, J., Slunt, H.H., Price, D.L. et al. (1998) Alzheimer amyloid protein precursor in the rat hippocampus: transport and processing through the perforant path. *J. Neurosci.* **18**, 9629–9637 https://doi.org/10.1523/JNEUROSCI.18-23-09629.1998

95 Penserga, T., Kudumala, S.R., Poulos, R. and Godenschwege, T.A. (2019) A role for Drosophila amyloid precursor protein in retrograde trafficking of L1-type cell adhesion molecule neuroglian. *Front. Cell. Neurosci.* **13**, 322 https://doi.org/10.3389/fncel.2019.00322

96 Godenschwege, T.A., Kristiansen, L.V., Uthaman, S.B., Hortsch, M. and Murphey, R.K. (2006) A conserved role for Drosophila neuroglian and human L1-CAM in central-synapse formation. *Curr. Biol.* **16**, 12–23 https://doi.org/10.1016/j.cub.2005.11.062

97 Gutierrez, D.A., Chandia-Cristi, A., Yanez, M.J. and Zanlungo, S. (2023) Alvarez AR. c-Abl kinase at the crossroads of healthy synaptic remodeling and synaptic dysfunction in neurodegenerative diseases. *Neural Regen. Res.* **18**, 237–243 https://doi.org/10.4103/1673-5374.346540

98 Leyssen, M., Ayaz, D., Hebert, S.S., Reeve, S., De Strooper, B. and Hassan, B.A. (2005) Amyloid precursor protein promotes post-developmental neurite arborization in the Drosophila brain. *EMBO J.* **24**, 2944–2955 https://doi.org/10.1038/sj.emboj.7600757

99 Dinamarca, M.C., Raveh, A., Schneider, A., Fritzius, T., Fruh, S., Rem, P.D. et al. (2019) Complex formation of APP with GABA(B) receptors links axonal trafficking to amyloidogenic processing. *Nat. Commun.* **10**, 1331 https://doi.org/10.1038/s41467-019-09164-3

100 Cvetkovska, V., Ge, Y., Xu, Q., Li, S., Zhang, P. and Craig, A.M. (2022) Neurexin-beta mediates the synaptogenic activity of amyloid precursor protein. *J. Neurosci.* **42**, 8936–8947 https://doi.org/10.1523/JNEUROSCI.0511-21.2022

101 Dean, C., Scholl, F.G., Choih, J., DeMaria, S., Berger, J., Isacoff, E. et al. (2003) Neurexin mediates the assembly of presynaptic terminals. *Nat. Neurosci.* **6**, 708–716 https://doi.org/10.1038/nn1074

102 Akaaboune, M., Allinquant, B., Farza, H., Roy, K., Magoul, R., Fiszman, M. et al. (2000) Developmental regulation of amyloid precursor protein at the neuromuscular junction in mouse skeletal muscle. *Mol. Cell. Neurosci.* **15**, 355–367 https://doi.org/10.1006/mcne.2000.0834

103 Strecker, P., Ludewig, S., Rust, M., Mundinger, T.A., Gorlich, A., Krachan, E.G. et al. (2016) FE65 and FE65L1 share common synaptic functions and genetically interact with the APP family in neuromuscular junction formation. *Sci. Rep.* **6**, 25652 https://doi.org/10.1038/srep25652

PORTLAND
PRESS

104   Wang, B., Yang, L., Wang, Z. and Zheng, H. (2007) Amyolid precursor protein mediates presynaptic localization and activity of the high-affinity choline transporter. *Proc. Natl Acad. Sci. U.S.A.* **104**, 14140–14145 https://doi.org/10.1073/pnas.0704070104

105   Wang, Z., Wang, B., Yang, L., Guo, Q., Aithmitti, N., Songyang, Z. et al. (2009) Presynaptic and postsynaptic interaction of the amyloid precursor protein promotes peripheral and central synaptogenesis. *J. Neurosci.* **29**, 10788–10801 https://doi.org/10.1523/JNEUROSCI.2132-09.2009

106   Ashley, J., Packard, M., Ataman, B. and Budnik, V. (2005) Fasciclin II signals new synapse formation through amyloid precursor protein and the scaffolding protein dX11/Mint. *J. Neurosci.* **25**, 5943–5955 https://doi.org/10.1523/JNEUROSCI.1144-05.2005

107   Choi, H.Y., Liu, Y., Tennert, C., Sugiura, Y., Karakatsani, A., Kroger, S. et al. (2013) APP interacts with LRP4 and agrin to coordinate the development of the neuromuscular junction in mice. *eLife* **2**. https://doi.org/10.7554/eLife.00220

108   Xie, Z., Dong, Y., Maeda, U., Xia, W. and Tanzi, R.E. (2007) RNA interference silencing of the adaptor molecules ShcC and Fe65 differentially affect amyloid precursor protein processing and Abeta generation. *J. Biol. Chem.* **282**, 4318–4325 https://doi.org/10.1074/jbc.M609293200

109   Suh, J., Lyckman, A., Wang, L., Eckman, E.A. and Guenette, S.Y. (2011) FE65 proteins regulate NMDA receptor activation-induced amyloid precursor protein processing. *J. Neurochem.* **119**, 377–388 https://doi.org/10.1111/j.1471-4159.2011.07419.x

110   Lee, J.H., Lau, K.F., Perkinton, M.S., Standen, C.L., Shemilt, S.J., Mercken, L. et al. (2003) The neuronal adaptor protein X11a reduces Ab levels in the brains of Alzheimer's APPswe Tg2576 transgenic mice. *J. Biol. Chem.* **278**, 47025–47029 https://doi.org/10.1074/jbc.M300503200

111   Saito, Y., Sano, Y., Vassar, R., Gandy, S., Nakaya, T., Yamamoto, T. et al. (2008) X11 proteins regulate the translocation of amyloid beta-protein precursor (APP) into detergent-resistant membrane and suppress the amyloidogenic cleavage of APP by beta-site-cleaving enzyme in brain. *J. Biol. Chem.* **283**, 35763–35771 https://doi.org/10.1074/jbc.M801353200

112   Mameza, M.G., Lockard, J.M., Zamora, E., Hillefors, M., Lavina, Z.S. and Kaplan, B.B. (2007) Characterization of the adaptor protein ARH expression in the brain and ARH molecular interactions. *J. Neurochem.* **103**, 927–941 https://doi.org/10.1111/j.1471-4159.2007.04854.x

113   Noviello, C., Vito, P., Lopez, P., Abdallah, M. and D'Adamio, L. (2003) Autosomal recessive hypercholesterolemia protein interacts with and regulates the cell surface level of Alzheimer's amyloid beta precursor protein. *J. Biol. Chem.* **278**, 31843–31847 https://doi.org/10.1074/jbc.M304133200

114   Jiang, J., Wang, Y., Hou, L., Fan, L., Wang, Q., Xu, Z. et al. (2013) Distinct roles of sAPP-alpha and sAPP-beta in regulating U251 cell differentiation. *Curr. Alzheimer Res.* **10**, 706–713 https://doi.org/10.2174/15672050113109990141

115   Tackenberg, C. and Nitsch, R.M. (2019) The secreted APP ectodomain sAPPalpha, but not sAPPbeta, protects neurons against Abeta oligomer-induced dendritic spine loss and increased tau phosphorylation. *Mol. Brain* **12**, 27 https://doi.org/10.1186/s13041-019-0447-2

116   Habib, A., Sawmiller, D. and Tan, J. (2017) Restoring soluble amyloid precursor protein alpha functions as a potential treatment for Alzheimer's disease. *J. Neurosci. Res.* **95**, 973–991 https://doi.org/10.1002/jnr.23823

117   Klevanski, M., Saar, M., Baumkotter, F., Weyer, S.W., Kins, S. and Muller, U.C. (2014) Differential role of APP and APLPs for neuromuscular synaptic morphology and function. *Mol. Cell. Neurosci.* **61**, 201–210 https://doi.org/10.1016/j.mcn.2014.06.004

118   Ott, M.O. and Bullock, S.L. (2001) A gene trap insertion reveals that amyloid precursor protein expression is a very early event in murine embryogenesis. *Dev. Genes Evol.* **211**, 355–357 https://doi.org/10.1007/s004270100158

119   Sarasa, M., Sorribas, V., Terradoa, J., Climent, S., Palacios, J.M. and Mengod, G. (2000) Alzheimer beta-amyloid precursor proteins display specific patterns of expression during embryogenesis. *Mech. Dev.* **94**, 233–236 https://doi.org/10.1016/s0925-4773(00)00297-5

120   Kesavapany, S., Banner, S.J., Lau, K.F., Shaw, C.E., Miller, C.C., Cooper, J.D. et al. (2002) Expression of the Fe65 adapter protein in adult and developing mouse brain. *Neuroscience* **115**, 951–960 https://doi.org/10.1016/s0306-4522(02)00422-0

121   Ho, A., Morishita, W., Hammer, R.E., Malenka, R.C. and Sudhof, T.C. (2003) A role for Mints in transmitter release: Mint 1 knockout mice exhibit impaired GABAergic synaptic transmission. *Proc. Natl Acad. Sci. U.S.A.* **100**, 1409–1414 https://doi.org/10.1073/pnas.252774899

122   Auderset, L., Cullen, C.L. and Young, K.M. (2016) Low density lipoprotein-receptor related protein 1 is differentially expressed by neuronal and glial populations in the developing and mature mouse central nervous system. *PLoS One* **11**, e0155878 https://doi.org/10.1371/journal.pone.0155878

123   Lau, K.F., McLoughlin, D.M., Standen, C.L., Irving, N.G. and Miller, C.C. (2000) Fe65 and X11beta co-localize with and compete for binding to the amyloid precursor protein. *Neuroreport* **11**, 3607–3610 https://doi.org/10.1097/00001756-200011090-00041

124   Chen, Y., Xu, J., Zhou, X., Liu, S., Zhang, Y., Ma, S. et al. (2019) Changes of protein phosphorylation are associated with synaptic functions during the early stage of Alzheimer's disease. *ACS Chem. Neurosci.* **10**, 3986–3996 https://doi.org/10.1021/acschemneuro.9b00190

125   Lau, K.F., Chow, W.N., Ngo, J.C.K., Chen, Y.W., Tam, V.K.M., Chan, E.H.Y. et al. (2019) FE65 serine-610 phosphorylation and its functional implications in Alzheimer disease amyloid precursor protein processing. *Hong Kong Med. J.* **25**, 44–47

126   Sakuma, M., Tanaka, E., Taru, H., Tomita, S., Gandy, S., Nairn, A.C. et al. (2009) Phosphorylation of the amino-terminal region of X11L regulates its interaction with APP. *J. Neurochem.* **109**, 465–475 https://doi.org/10.1111/j.1471-4159.2009.05988.x

127   Cheung, H.N., Dunbar, C., Morotz, G.M., Cheng, W.H., Chan, H.Y., Miller, C.C. et al. (2014) FE65 interacts with ADP-ribosylation factor 6 to promote neurite outgrowth. *FASEB J.* **28**, 337–349 https://doi.org/10.1096/fj.13-232694

128   Zhai, Y., Chan, W.W.R., Li, W. and Lau, K.F. (2022) ARNO is recruited by the neuronal adaptor FE65 to potentiate ARF6-mediated neurite outgrowth. *Open Biol.* **12**, 220071 https://doi.org/10.1098/rsob.220071

129   Wakutani, Y., Watanabe, K., Adachi, Y., Wada-Isoe, K., Urakami, K., Ninomiya, H. et al. (2004) Novel amyloid precursor protein gene missense mutation (D678N) in probable familial Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **75**, 1039–1042 https://doi.org/10.1136/jnnp.2003.010611

130   Eriksson, P.S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D.A. et al. (1998) Neurogenesis in the adult human hippocampus. *Nat. Med.* **4**, 1313–1317 https://doi.org/10.1038/3305

131   Wang, S., Bolos, M., Clark, R., Cullen, C.L., Southam, K.A., Foa, L. et al. (2016) Amyloid beta precursor protein regulates neuron survival and maturation in the adult mouse brain. *Mol. Cell. Neurosci.* **77**, 21–33 https://doi.org/10.1016/j.mcn.2016.09.002

132   Schinder, A.F., Trinchero, M.F. and Groisman, A.I. (2020) Chapter 10 - Synaptogenesis in the adult CNS—Hippocampus. In *Synapse Development and Maturation* (Rubenstein, J., Rakic, P., Chen, B., Kwan, K.Y., Cline, H.T., Cardin, J., eds), pp. 235–253, Academic Press, Cambridge, Massachusetts, U.S.

133   Moreno-Jimenez, E.P., Flor-Garcia, M., Terreros-Roncal, J., Rabano, A., Cafini, F., Pallas-Bazarra, N. et al. (2019) Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat. Med.* **25**, 554–560 https://doi.org/10.1038/s41591-019-0375-9

134   Winner, B., Melrose, H.L., Zhao, C., Hinkle, K.M., Yue, M., Kent, C. et al. (2011) Adult neurogenesis and neurite outgrowth are impaired in LRRK2 G2019S mice. *Neurobiol. Dis.* **41**, 706–716 https://doi.org/10.1016/j.nbd.2010.12.008