

PRIMER

Amyloid precursor protein and neural development

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ABSTRACT

Interest in the amyloid precursor protein (APP) has increased in recent years due to its involvement in Alzheimer's disease. Since its molecular cloning, significant genetic and biochemical work has focused on the role of APP in the pathogenesis of this disease. Thus far, however, these studies have failed to deliver successful therapies. This suggests that understanding the basic biology of APP and its physiological role during development might be a crucial missing link for a better comprehension of Alzheimer's disease. Here, we present an overview of some of the key studies performed in various model organisms that have revealed roles for APP at different stages of neuronal development.

KEY WORDS: Amyloid precursor protein, Neural development, Axonal outgrowth, Synapse formation

Introduction

Alzheimer's disease (AD) is characterized by a progressive degeneration of neurons, which results in cognitive deficiency, behavioral disturbance and neuropsychiatric symptoms (Arlard and Cummings, 2004). AD is currently incurable and is considered to be the most common neurodegenerative dementia, with ~30 million patients worldwide (Barnes and Yaffe, 2011). As originally described by Alois Alzheimer in 1906, two neuropathological hallmarks characterize AD: intraneuronal bundles, known as neurofibrillary tangles (NFTs); and amyloid plaques, which are mainly composed of the peptide amyloid β (A β). The fact that NFTs are not specific to AD and are found in other neurodegenerative diseases, such as Parkinson's disease (Perl, 2000), has pushed AD research towards intensively investigating an amyloidogenic hypothesis for the origin of AD.

The A β peptide is generated from amyloid precursor protein [also known as amyloid beta (A4) precursor protein, APP], which is a precursor protein that undergoes sequential cleavages by β and γ secretases (De Strooper et al., 2010). APP has been shown to be involved in many biological processes and is implicated in various signaling pathways. However, its basic physiological function in developing and adult organisms remains unclear. Many APP loss- and gain-of-function approaches in model organisms, such as *Caenorhabditis elegans*, *Drosophila melanogaster*, zebrafish and mouse, have been used to model AD. However, none of these models fully recapitulates all aspects of the disease. Nonetheless, studies using these model organisms have furthered our understanding of the physiological function of APP in the brain.

In this Primer, we review these studies and discuss the role of APP, its products and its homologs at different stages of neuronal development.

Domain structure and processing of APP

Human APP belongs to an evolutionarily conserved family of type I transmembrane glycoproteins (Fig. 1) that also includes the paralogs amyloid precursor-like proteins 1 and 2 (APLP1 and APLP2), which show functional redundancy but lack the A β sequence (Goldgaber et al., 1987; Wasco et al., 1993). Several alternatively spliced isoforms of APP have been identified in humans (Beyreuther et al., 1993). The conservation of APP extends to invertebrates, including the fruit fly *D. melanogaster* and the worm *C. elegans*, with its respective orthologs β amyloid protein precursor-like (APPL) and APP-like 1 (APL-1) (Rosen et al., 1989; Daigle and Li, 1993). Unlike the fruit fly genome, which encodes only one APP homolog, the zebrafish genome encodes two APP variants: Appa and Appb. Appa is more similar to the human APP770 isoform, whereas Appb, which is abundantly expressed in the zebrafish brain, resembles the human APP695 isoform (Joshi et al., 2009; Lee and Cole, 2007). All of these proteins share several conserved domains within their large extracellular regions, and harbor a short cytoplasmic domain that displays the highest homology (Gralle and Ferreira, 2007). Although vertebrate models may provide a closer match to humans (Fig. 1), invertebrate models such as *D. melanogaster* and *C. elegans* offer powerful and tractable systems with which to investigate the function of APP orthologs *in vivo* and to understand how this gene is involved in the pathogenesis of AD. In addition to the tractability of these models, the fact that they have a single APP homolog simplifies the genetic analysis of the gene family function.

APP can undergo amyloidogenic and non-amyloidogenic processing depending on the secretases that cleave it (Ling et al., 2003). In the amyloidogenic pathway (Fig. 2, right), APP is initially cleaved by β -secretase to produce a soluble secreted form of APP (sAPP β) and a C-terminal fragment (β APP-CTF). The subsequent cleavage of β APP-CTF by γ -secretase yields the A β peptide and the amyloid precursor protein intracellular domain (AICD). In the non-amyloidogenic pathway (Fig. 2, left), APP is first cleaved by α -secretase within the A β sequence to generate the soluble secreted sAPP α fragment and the membrane-tethered α APP-CTF. This is followed by γ -secretase cleavage of α APP-CTF, resulting in release of the P3 peptide and AICD.

Although A β may be fundamental to AD pathology, the evolutionary conservation of APP and the absence of the A β sequence in almost all APP homologs signify that amyloidogenesis is unlikely to be the main function of this family of proteins (Hardy and Selkoe, 2002). In line with this, recent evidence indicates that APP is a key developmental gene that regulates the generation of neurons, their differentiation and migration. In addition, APP has been shown to be involved in neurite outgrowth and guidance and in the regulation of synaptic function. These developmental roles of APP are further discussed below.

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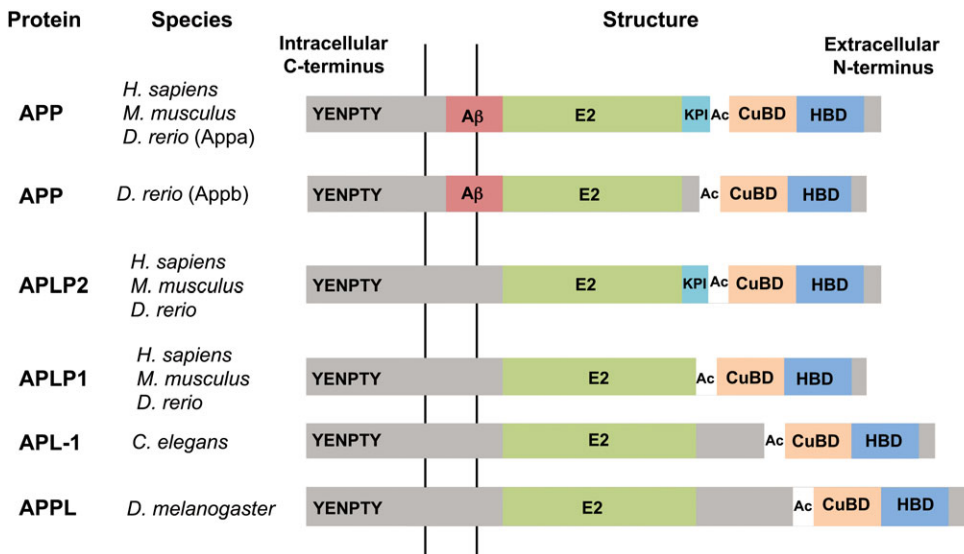


Fig. 1. The domain structure of APP family members in model organisms. The domain structure of human (*H. sapiens*) APP and its homologs in the mouse (*M. musculus*), zebrafish (*D. rerio*), worm (*C. elegans*) and fruit fly (*D. melanogaster*) is shown. The extracellular region contains an E2 domain, an acidic (Ac) domain, a copper-binding domain (CuBD) and a heparin-binding domain (HBD), all of which are conserved across species. A Kunitz protease inhibitor (KPI) domain, which is subject to alternative splicing, is also found in APP and APLP2. The intracellular domain shows the highest homology and contains the YENPTY motif that is conserved across homologs. The A β sequence is only present in APP.

APP function in neurogenesis

APP has been shown to regulate various aspects of neurogenesis, and this is reflected in its early expression during brain development. Indeed, *App* mRNA was shown to be expressed by embryonic day (E) 9.5 in the mouse neural tube, which coincides with the peak of neural differentiation and neurite outgrowth (Salbaum and Ruddle, 1994). Moreover, immunocytochemistry detected abundant APP in radial glial cells in fetal mouse brain (Trapp and Hauer, 1994). Despite the early expression of APP, mice carrying a deletion in the *App* gene do not show severe brain phenotypes, probably owing to functional compensation by other APP family members (Zheng et al., 1995; Heber et al., 2000). The fact that *Aplp2*^{-/-} *Aplp1*^{-/-} mice and *Aplp2*^{-/-} *App*^{-/-} mice are early postnatal lethal strongly indicates redundancy between APLP2 and the other family members (Heber et al., 2000).

A number of studies have implicated APP and its processed forms in neuronal proliferation and division. For example, sAPP α , the product of APP cleavage by α -secretase, shows similar functions to growth factors and increases the *in vitro* proliferation of embryonic neural stem cells (NSCs). This observation comes from early studies showing that sAPP α stimulates the proliferation of NSCs isolated from embryonic rat neocortex (Hayashi et al., 1994; Ohsawa et al.,

1999). More recently, Caillé et al. investigated the role of sAPP α in adult neurogenesis and found that the infusion of *App* antisense oligonucleotide into the lateral ventricles of adult mice resulted in a reduction in the proliferation of neural progenitor cells (NPCs) in the subventricular zone (SVZ), a region considered to be one of the two pools of NSCs in the adult nervous system. This phenotype can be rescued by infusion of sAPP α (Caillé et al., 2004). In parallel, recent evidence shows that inhibiting α -secretase activity reduces NPC proliferation *in vitro*, and this proliferation can be rescued by adding recombinant sAPP α to the culture medium (Demars et al., 2011). Little is currently known about the mechanism by which sAPP α induces NSC division. However, it is noteworthy that sAPP α bears a cysteine-rich domain that is highly conserved across APP homologs (Rossjohn et al., 1999) and resembles domains in other growth factors, suggesting that sAPP α might function as a growth factor to stimulate intracellular signaling.

The role of AICD remains controversial in APP biology due to the assumption, by analogy with Notch signaling, that AICD is able to regulate gene transcription. Some groups have proposed that AICD can promote gene transcription (Cao and Südhof, 2001), whereas others have demonstrated that AICD is not directly involved in a nuclear signaling pathway (Hébert et al., 2006). Despite the

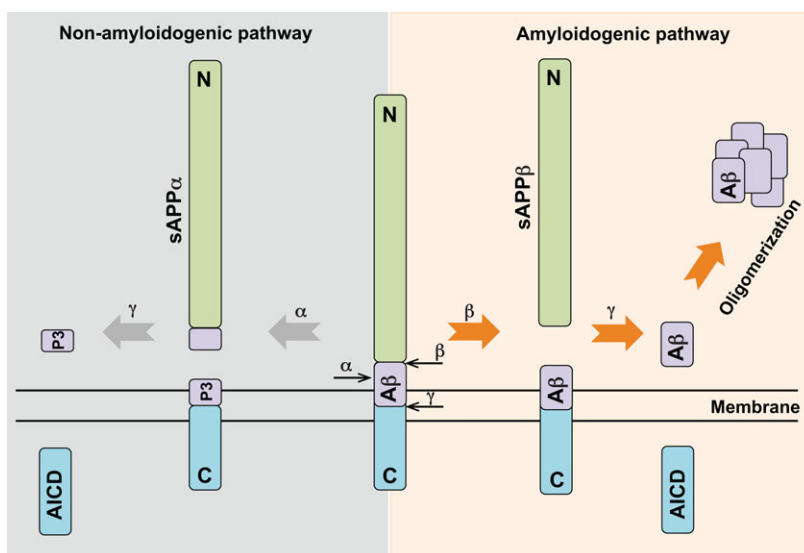


Fig. 2. The proteolytic processing of APP. APP can be cleaved by α -, β - and γ -secretases; the cleavage sites of these proteases are indicated in the full-length APP shown in the center of the figure. APP can undergo amyloidogenic (right) or non-amyloidogenic (left) processing. In the amyloidogenic pathway, cleavage by β -secretase results in the formation of soluble APP β (sAPP β) and β APP-CTF. The subsequent action of γ -secretase on β APP-CTF releases A β from the amyloid precursor protein intracellular domain (AICD). In the non-amyloidogenic pathway, cleavage by α -secretase prevents the formation of A β ; α -secretase cleaves within the A β sequence, giving rise to sAPP α and the membrane-tethered α APP-CT, which in turn is cleaved by γ -secretase resulting in release of the P3 peptide and AICD.

discrepancy regarding the role of AICD in transcription, studies that have examined the role of AICD in NPC proliferation are worth highlighting. In contrast to the role of sAPP α in proliferation, AICD has been suggested to be a negative regulator of NPC proliferation. This assumption comes from data showing that AICD negatively regulates transcription of the gene encoding epidermal growth receptor (EGFR), which is known to drive the proliferation of NPCs (Zhang et al., 2007; Ayuso-Sacido et al., 2010). Moreover, *App* knockout (KO) mice expressing AICD show a reduction in NPC proliferation and survival in the dentate gyrus, which is mediated through induction of neuroinflammation (Ghosal et al., 2010).

In contrast to the widely accepted role of sAPP α in NPC proliferation, the physiological function of A β in the context of NPC proliferation remains ambiguous. On the one hand, it was demonstrated that the treatment of human cortical NPC cultures *in vitro* with A β reduces NPC proliferation (Haughey et al., 2002). On the other hand, studies have shown that A β stimulates the proliferation of NPCs derived from the adult murine SVZ (López-Toledano and Shelanski, 2004). It is possible that these contradictory results are due to the different culture systems or the different A β isoforms used. Furthermore, it is noteworthy that these studies might not reflect the endogenous role of A β , as they were performed using exogenous A β peptide.

Because the early expression of APP corresponds to the timing of neural differentiation, it was also suggested that APP and/or its metabolites might play a role in neuronal differentiation. In human embryonic stem cells (hESCs), the overexpression of APP or its soluble forms causes rapid and robust differentiation toward a neural fate (Freude et al., 2011). Furthermore, in adult bone marrow progenitor cells, sAPP α enhances transdifferentiation to neuronal phenotypes (Chen et al., 2006). The role of A β in the fate determination of NPCs has also been described, as treatment of SVZ-derived NPCs with the A β ₄₂ isoform pushes differentiation toward a neuronal fate (Heo et al., 2007). Finally, a recent study suggests that, in mice, the APP paralog APLP2 might play a role in NSC differentiation (Shariati et al., 2013).

Another key factor in the integration of neurons into the proper functional circuits is the migration to their terminal positions. Young-Pearse et al. (2007) have shown that the acute elimination of APP expression in rodent NPCs (using *in utero* electroporation of shRNAs) prevented cells of the cortical ventricular zone from entering the cortical plate. In addition, the overexpression of APP in NPCs accelerated their migration into the cortex. Following this work, Rice et al. showed that pancortins, which are glycoproteins highly expressed in the developing cortex, functionally interact with APP to regulate NPC migration in the mammalian cortex (Rice et al., 2012). Taken together, these results strongly suggest that APP can regulate neuronal migration in the developing cortex (Young-Pearse et al., 2007). However, contrary to those results, Herms et al. have reported that in *App Aplp1 Aplp2* triple KO mice, neurons overmigrate and accumulate in the marginal zone, resembling human type 2 cobblestone lissencephaly (Herms et al., 2004). The divergence in these results might indicate different roles for APPs and APLPs in regulating distinct processes in different regions of the cortex. In line with this, studies from the Copenhagen laboratory suggest that mouse APP and fly APPL regulate neural migration through interactions with heterotrimeric G proteins (Swanson et al., 2005; Ramaker et al., 2013).

The role of APP in neurite outgrowth and guidance

Numerous *in vitro* studies have established that APP plays a role in neurite growth. However, the results of such studies are sometimes

inconsistent with regards to whether APP enhances or inhibits neurite elongation. This inconsistency is dependent on multiple factors, including the type of cultured cells used, the substrates on which the cells are plated, and the timing of analysis after plating. Nonetheless, *in vitro* studies have provided substantial evidence regarding the role of APP in increasing neurite length and branching, either independently or through its interaction with other proteins such as Disabled-1 (Milward et al., 1992; Hoareau et al., 2008). In addition, a role for APP products such as sAPP α/β and AICD in inducing neurite outgrowth has been reported in *in vitro* work (Chasseigneaux et al., 2011; Zhou et al., 2012). However, this section will focus on results generated from *in vivo* studies of APP and neurite outgrowth and guidance (as summarized in Table 1).

D. melanogaster has been used extensively to study the role of the APP homolog APPL in the context of axonal growth. Recently, it has been shown that *Appl* null flies (*Appl*^Δ) display developmental axonal growth defects in mushroom bodies, which house a neuronal population that is important for learning and memory (Soldano et al., 2013), as well as in retinal axons (Mora et al., 2013). The expression of full-length APPL, but not sAPPL nor a membrane-tethered form lacking the conserved C-terminus, rescued this phenotype, suggesting that the APPL C-terminus is crucial for its function. Moreover, the study showed that APPL acts by modulating Wnt-planar cell polarity (Wnt-PCP) signaling, which was already known from fly and mouse work to be involved in axonal outgrowth and guidance (Srahna et al., 2006; Shafer et al., 2011; Ng, 2012). In previous work, the overexpression of human APP and APPL in fly neurons resulted in an increase in axonal extension of sLNv neurons, a group of neurons in the fly brain important for the regulation of circadian rhythm (Leyssen et al., 2005). APP domains were mapped and the highly conserved YENPTY motif located at the C-terminus of the protein was identified as responsible for the axonal outgrowth gain-of-function phenotype. Furthermore, in zebrafish, a developmental axonal outgrowth defect in facial branchiomotor neurons Vp and VII was reported following the knockdown (KD) of *Appb* (Song and Pimplikar, 2012). Interestingly, human APP or zebrafish *Appb*, but neither the extracellular domain of *Appb*, which is equivalent to sAPP β , nor the membrane-tethered form *Appb*-C99, could rescue the defective phenotype, implying that both the N-terminal and C-terminal domains of the protein are needed for this function.

Table 1. Axon growth and guidance phenotype observed in APP loss-of-function studies in model organisms

Organism	Gene	Axon growth phenotype	References
<i>D. melanogaster</i>	<i>Appl</i>	<i>Appl</i> KO results in developmental axonal growth defects in mushroom body neurons	(Soldano et al., 2013)
<i>D. rerio</i>	<i>appb</i>	<i>Appb</i> KD leads to a developmental defect in axonal growth of the facial branchiomotor neurons Vp and VII	(Song and Pimplikar, 2012)
<i>M. musculus</i>	<i>App</i>	Functional reduction of APP results in reduced size of the ventral hippocampal commissure	(Magara et al., 1999)
		<i>App</i> ^{-/-} embryos display axon guidance defects of the commissures	(Rama et al., 2012)
		APP reduction by shRNA results in longer axons than in the control	(Young-Pearse et al., 2008)

A role for APP in axonal growth and guidance has also been provided by studies in mice. Magara et al., for example, showed that transgenic mice lacking functional APP display a smaller ventral hippocampal commissure (Magara et al., 1999). A more recent study (Rama et al., 2012) further elucidated the mechanism by which APP induces abnormalities in commissural neuron extension and guidance. This study showed that *App*^{-/-} mouse embryos do not show major defects in axon extension but display an axon guidance phenotype that is characterized by thickened axonal bundles. Based on gain- and loss-of-function experiments, the authors postulated that APP mediates axon guidance by being part of the DCC complex, which was shown to mediate netrin 1 signaling during commissural axon navigation (Rama et al., 2012). In previous work, the same group showed that netrin 1 can act as a functional ligand for APP and negatively regulates the formation of A β (Lourenço et al., 2009). Based on these studies, the authors proposed that DCC acts as a modulator and APP as a receptor for netrin 1, in order to maintain proper guidance for commissural axons. However, contrary to these results, another study showed that *in utero* electroporation of APP shRNA into NPCs lining the lateral ventricle of rat embryos, which were cultured 2 days after electroporation, displayed longer axons than control neurons (Young-Pearse et al., 2008). The above mentioned studies that tackled the role of APP in neurite outgrowth have identified a number of binding partners for APP, including Van Gogh, Abelson tyrosine kinase, netrin 1 and integrin β 1, and, interestingly, these proteins were previously linked to cytoskeletal rearrangement. This suggests that APP could modulate different signaling pathways, perhaps depending on cellular and developmental context, to induce modifications in cell motility leading to neurite outgrowth.

APP function in axonal transport and synaptogenesis

In flies, *Appl* deletion causes a reduction in the number of synaptic boutons at neuromuscular junctions (NMJs), whereas its overexpression increases synaptic bouton numbers, suggesting that APPL is important for the development of NMJs (Torroja et al., 1999). The mechanism by which APPL functions at the level of the NMJ has been investigated further: it was shown that APPL and the adhesion molecule Fasciclin 2 (Fas2) form a complex, and that APPL-Fas2 signaling depends on the interaction between APPL and the APPL-binding protein X11L (also known as Mint) to regulate synapse formation (Ashley et al., 2005).

In the human and rat brain, APP was shown to undergo rapid axonal transport to synaptic sites (Koo et al., 1990). Moreover, APP was found in vesicular elements of dendrites and axons (Schubert et al., 1991),

suggesting a possible role for APP in synaptic activity. At the level of the NMJs, APP family members were shown to be important for the postnatal maturation and maintenance of the neuromuscular synapse (Weyer et al., 2011). In addition, the *App Appl2* double KO exhibits impaired synaptic structure, defective synaptic transmission, a reduced number of presynaptic vesicles and defective neurotransmitter release (Wang et al., 2005); it was also shown that APP, as an adhesion molecule, is needed in both pre- and post-synaptic regions to regulate the assembly and function of the neuromuscular synapse (Wang et al., 2009). The importance of APP as a cell adhesion molecule in synapse formation is also supported by the fact that APP family members are enriched in synaptic membrane compartments, where APP and APLP1 form a heteromeric complex (Soba et al., 2005). APP also regulates synaptogenesis in the central nervous system; the decrease in dendritic length and complexity in *App* single KO mice correlated with impaired synaptic function (Tyan et al., 2012). Interestingly, sAPP α restored the dendritic spine number in *App* KO mice, supporting the notion of sAPP α having neurotrophic properties. In accordance with this study, infusion of sAPP α into the brain of non-transgenic mice or overexpression of the α -secretase ADAM10 resulted in increased numbers of presynaptic boutons (Bell et al., 2008).

Like APPL, which was shown to be important for learning in flies (Goguel et al., 2011), APP and APLP2 were reported to be important for spatial learning and synaptic plasticity (Weyer et al., 2011). *App* KO mice showed spatial navigation defects that correlated with long-term potentiation deficits (Ring et al., 2007). Interestingly, the learning defects were rescued in mice expressing solely sAPP α , indicating the importance of this soluble form in learning and synaptic plasticity. It should also be noted that, in contrast to the *in vivo* studies mentioned above that highlight the importance for APP family proteins in neuronal development and function, cultured neurons derived from stem cells lacking the three APP family members (APP, APLP1 and APLP2) were capable of extending long neurites and forming active synapses (Bergmans et al., 2010). These observations highlight the importance of studying APP function in living model organisms.

APP function in morphogenesis

The tight connection between APP and AD has directed the majority of studies investigating APP biology towards its role in the brain and in AD pathology. However, a number of studies have shown that APP is also involved in several other developmental processes. One of these is convergent extension (CE), which is the process by which cells in an epithelial sheet move and promote tissue elongation by intercalating between adjacent cells (Tada and

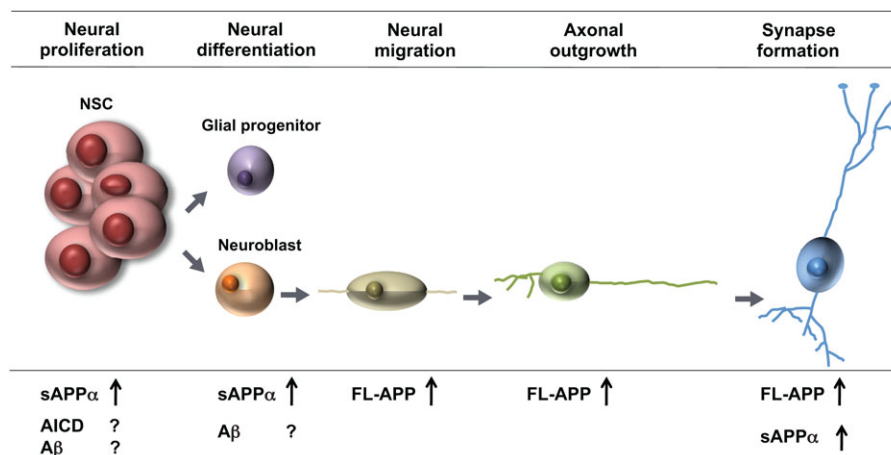


Fig. 3. Summary of the roles of APP and its metabolites during neural development. APP and APP metabolites play important roles during various stages of neural development, ranging from the proliferation, differentiation and migration of NSCs and neural progenitor cells to the formation of a functional synapse. APP metabolites that have a positive effect on these various processes are indicated by upward arrows. Metabolites with unknown or unclear effects on specific processes are indicated by question marks.

Heisenberg, 2012). In zebrafish, it was demonstrated that Appb KD using antisense morpholino oligonucleotides resulted in CE defects, including a short body axis, a short curly tail and wide somites (Joshi et al., 2009). Interestingly, the expression of human APP, but not the AD variant APP_{swe}, could rescue this phenotype. The precise mechanism by which APP affects the CE process is still unclear. One possibility is that it involves the interaction of APP with the Wnt-PCP pathway (Fanto and McNeill, 2004).

APP has also been shown to be involved in developmental processes in *C. elegans*. Hornsten et al. showed that the complete loss of APL-1 led to a lethal molting defect during the first to second larval stage transition, and that the expression of the extracellular domain of APL-1 was sufficient to rescue this lethality (Hornsten et al., 2007). In accordance with this result, recent work has shown that APL-1 is required for every transitional molt (Ewald et al., 2012).

Conclusions

APP has proven to be a key factor in establishing and maintaining neuronal architecture. Evidence from different model organisms has demonstrated that APP orchestrates neuronal development from early stages, when deciding neuronal fate, until the establishment of a functional synapse (Fig. 3). Studying APP biology using KO animals has thus greatly enhanced our understanding of the molecular *in vivo* functions of this protein. However, much remains to be elucidated, especially in terms of the molecular and cellular mechanisms of APP function. The relatively subtle phenotypes caused by APP loss of function suggest that its main role is to increase the robustness of brain development and function. It is therefore useful to think of APP as a permissive factor for various neurodevelopmental and neural circuit processes, rather than as an instructive protein that acts in specific developmental signals. It is thus worth considering whether compromising this function in brain protection might underlie AD. In such a model, AD, whether familial or sporadic, would be the result of a slow decline in the brain's capacity to deal with the normal stresses of ageing due to the aberrant activity of APP. Because APP is itself a neuronal stress-response protein, one imagines that in a disease context this results in a vicious cycle of ever increasing neuronal stress until the onset of neuronal degeneration. In this context, it seems that the crucial next step would be to ask which, if any, of the physiological functions and molecular interactions of APP *in vivo* are relevant to the onset of AD pathology. Experiments that test AD variants of APP using careful quantitative assays of the processes in which APP has been implicated in ageing animal models might be an important future direction of research. To this end, identifying specific, *in vivo* validated biochemical interactions that can be assayed quantitatively in animal models, but also in patient-derived tissue, would be of great value to the field.

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Competing interests

The authors declare no competing financial interests.

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