Published in final edited form as:
J Neurochem. 2012 January ; 120(Suppl 1): 9–21. doi:10.1111/j.1471-4159.2011.07519.x.

Proteolytic processing of Alzheimer's β-amyloid precursor protein

Han Zhang[*,†,1], **Qilin Ma**[‡,1], **Yun-wu Zhang**[*], and **Huaxi Xu**[*,†]

[*]Fujian Provincial Key Laboratory of Neurodegenerative Disease and Aging Research, College of Medicine, Xiamen University, Xiamen, Fujian 361005, China

[†]Neurodegenerative Disease Research Program, Sanford-Burnham Medical Research Institute, 10901 North Torrey Pines Road, La Jolla 92037, CA, USA

[‡]Department of Neurology, the First Affiliated Hospital of Xiamen University, Xiamen, Fujian 361005, China

Abstract

β–amyloid precursor protein (APP) is a critical factor in the pathogenesis of Alzheimer's disease (AD). APP undergoes posttranslational proteolysis/processing to generate the hydrophobic β-amyloid (Aβ) peptides. Deposition of Aβ in the brain, forming oligomeric Aβ and plaques, is identified as one of the key pathological hallmarks of AD. The processing of APP to generate Aβ is executed by β- and γ-secretase and is highly regulated. Aβ toxicity can lead to synaptic dysfunction, neuronal cell death, impaired learning/memory and abnormal behaviors in AD models *in vitro* and *in vivo*. Aside from Aβ, proteolytic cleavages of APP can also give rise to the APP intracellular domain (AICD), reportedly involved in multiple types of cellular events such as gene transcription and apoptotic cell death. In addition to amyloidogenic processing, APP can also be cleaved by α-secretase to form a soluble or secreted APP ectodomain (sAPP-α) that has been shown to be mostly neuro-protective. In this review, we describe the mechanisms involved in APP metabolism and the likely functions of its various proteolytic products to give a better understanding of the patho/physiological functions of APP.

Keywords

β–amyloid precursor protein; α-secretase; β-secretase; γ-secretase; caspase

Alzheimer's disease (AD), first officially described by the German psychiatrist and neuropathologist Alois Alzheimer in 1906, is the most common form of dementia. Characterized by progressive cognitive impairment, loss of memory and abnormal behavior, AD generally affects people over the age of 65. However, around 5% of AD patients develop the disease phenotype at a much younger age (~40 to 50 years old) and are classified as early-onset, most of which are also familial cases. Plaques consisting of β–amyloid (Aβ) peptide (Selkoe 1998), neurofibrillary tangles (NFTs) consisting largely of hyperphosphorylated microtubule-associated tau protein (Buee *et al.* 2000; Gendron and Petrucelli 2009) and neuron loss in the hippocampus and cortex regions are the major pathological hallmarks of Alzheimer's disease. As Aβ is believed to play a crucial role in the

Address correspondence and reprint requests to Dr. Huaxi Xu, Sanford-Burnham Medical Research Institute, 10901 N. Torrey Pines Rd., La Jolla, CA 92037, USA. Telephone: +1 858 7955246; Fax: +1 858 7955273. xuh@sanfordburnham.org.
[1]These authors contributed equally to this study.

The authors declare no conflict of interest with respect to the research reported herein.

pathogenesis of AD, its precursor protein APP has become one of the most studied proteins in the field of AD research.

Basic knowledge of APP

The amyloid plaques associated with AD were first purified and found to consist of multimeric aggregates of Aβ polypeptide containing about 40 amino acid residues in the mid-1980s (Glenner and Wong 1984; Masters *et al.* 1985). Cloning of the complementary DNA (cDNA) of Aβ revealed that Aβ is derived from a larger precursor protein (Tanzi *et al.* 1987). The full-length cDNA of the amyloid precursor protein (APP) was later isolated and sequenced and APP was predicted to be a glycosylated integral membrane cell surface receptor protein with 695 amino acids (Kang *et al.* 1987). The Aβ peptide was found to be a cleavage product derived from the transmembrane domain of this large precursor protein.

The *APP* gene is located on chromosome 21 and contains 18 exons. Although alternative splicing of transcripts from the single *APP* gene results in several isoforms of the gene product, APP695, whose encoding cDNA lacks the gene sequence from exons 7 and 8, is preferentially expressed in neurons (Sandbrink *et al.* 1994). APP751, lacking exon 8, and APP770, encoded with all 18 exons, are predominant variants elsewhere (Yoshikai *et al.* 1990). Two homologues of APP were also identified and named APP-like protein 1 and 2 (APLP1 and APLP2) (Wasco *et al.* 1992; Wasco *et al.* 1993; Coulson *et al.* 2000). APLP2, similarly to APP, is expressed ubiquitously while APLP1 is only expressed in the brain and is only found in mammals.

The APP protein is a type I integral membrane protein with a large extracellular portion, a hydrophobic transmembrane domain, and a short C-terminus designated the APP intracellular domain (AICD). The extracellular portion of APP contains E1 and E2 domains and a Kunitz protease inhibitor (KPI) domain that is missing in APP695 (Kang and Muller-Hill 1990;Rohan de Silva *et al.* 1997). The E1 domain is reported to function as the major interaction interface for dimerization of cellular APP/APLPs (Soba *et al.* 2005). Although trans-dimerization of the E2 domain is also observed in X-ray structures (Wang and Ha 2004), biochemical assays have failed to confirm such a trans-dimerization (Soba *et al.* 2005). The levels of APP isoforms with a KPI domain seem to be elevated in patients with AD (Menendez-Gonzalez *et al.* 2005) and a splicing shift in neurons from APP695 to KPI-containing APP isoforms, along with increased Aβ generation, is observed when the NMDA receptor is activated (Bordji *et al.* 2010). These studies suggest that an alteration in APP splicing may contribute to disease pathogenesis.

APLP1 and APLP2 are both type I integral membrane proteins and share conserved structures with APP, including a large extracellular motif containing the E1 and E2 domains and a short intracellular domain. However, the transmembrane domain is not conserved among APP and APLPs and the Aβ sequence is unique to APP. In addition, APLP1 does not possess the KPI domain due to a lack of the encoding exon in the *APLP1* gene.

Manipulations of the APP/APLPs genes suggest that they are partially functionally redundant. Upon individual deletion of any of these three genes, mice are viable with only relatively subtle abnormalities (Zheng *et al.* 1995; Dawson *et al.* 1999). However, APP/APLP2, APLP1/APLP2 double knockout or APP/APLP1/APLP2 triple knockout mice show early postnatal lethality. Interestingly, APP/APLP1 double knockout mice are viable, indicating a crucial function of APLP2 in the absence of either APP or APLP1 (von Koch *et al.* 1997; Heber *et al.* 2000; Herms *et al.* 2004). Although it was reported that neurons generated from APP/APLP1/APLP2 triple knockout embryonic stem cells behave normally *in vitro* and *in vivo* (Bergmans *et al.* 2010), abnormal developments in the peripheral and central nervous system were repeatedly observed in both APP/APLP2 double knockout mice

and APP/APLP1/APLP2 triple knockout mice (Wang *et al.* 2005; Yang *et al.* 2005; Wang *et al.* 2007; Wang *et al.* 2009). Studies reported that the APP/APLP2 double knockout results in impaired neuromuscular junctions, indicating that the trans-synaptic interaction of APP is necessary for the proper development of motor neurons. Cortical dysplasia due to defective neuronal migration was also shown in APP/APLP1/APLP2 triple knockout mice (Herms *et al.* 2004). Although the physiological functions of APP/APLPs have not been well characterized, these loss-of-function phenotypes suggest the comprehensive involvement of these proteins during development.

APP processing

APP undergoes posttranslational processing, involving several different secretases and proteases, via two major pathways. In the non-amyloidogenic pathway, APP is sequentially cleaved by α-secretase and γ-secretase. α-cleavage, which cuts APP at the 17th amino acid inside the Aβ peptide sequence (Fig. 1), releases a large secreted extracellular domain (sAPP-α) and a membrane-associated C-terminal fragment consisting of 83 amino acids (C83). APP C83 is further cleaved by γ-secretase to release a P3 peptide and the APP intracellular domain (AICD), both of which are degraded rapidly. In the amyloidogenic pathway, APP is primarily processed by β-secretase at the 1st residue or at the 11th residue (so called β' site) of the Aβ peptide sequence (Fig. 1), shedding sAPP-β and generating a membrane associated C terminal fragment consisting of 99 amino acids (C99) (Sarah and Robert 2007). γ-secretase further cleaves C99 to release AICD and the amyloidogenic Aβ peptide which aggregates and fibrillates to form amyloid plaques in the brain.

α-secretase and α-cleavage

Since APP was found to be constitutively cleaved at the α-site to yield sAPP-α (Esch *et al.* 1990), three members of the ADAMs (a disintegrin and metalloproteinase), ADAM-10, ADAM-17 and ADAM-9 have been proposed as the α-secretase (Buxbaum *et al.* 1998; Koike *et al.* 1999; Lammich *et al.* 1999).

ADAMs are type I integral membrane proteins that belong to the zinc protease super family and have been implicated in the control of cytokine and growth factor shedding. ADAM10 is widely expressed in the brain and in other tissues (Chantry and Glynn 1990; Howard *et al.* 1996) and a several fold increase in sAPP-α levels in cell lines overexpressing ADAM10 can be observed (Lammich *et al.* 1999). Moderate neuronal overexpression of human ADAM10 increases sAPP-α production while reducing Aβ generation/plaque formation in mice carrying the human APP V717I mutation, while expression of a catalytically-inactive form of the ADAM10 mutation increases the size and number of amyloid plaques in mouse brains (Lammich *et al.* 1999). These findings suggest that ADAM10 may be responsible for constitutive α-cleavage activity. On the other hand, although sAPP-α generation is not affected in ADAM9/17 knock-down cell lines nor in mice carrying deficient ADAM9/17 genes (Weskamp *et al.* 2002; Kuhn *et al.* 2010), overexpression of ADAM9/17 does increase the level of sAPP-α under some conditions, suggesting that ADAM9 and ADAM17 are more likely involved in the regulated α-cleavage of APP rather than in constitutive α-cleavage.

In addition to APP, ADAMs have many other substrates (Qiang *et al.* 2009; Altmeppen *et al.* 2011). For example, ADAM17 has been identified as the protease responsible for shedding of the transmembrane form of tumor necrosis factor-α at its physiological processing site (Black *et al.* 1997; Moss *et al.* 1997). ADAM17 also cleaves the epidermal growth factor (EGF) family members (Peschon *et al.* 1998; Lee *et al.* 2003) and ADAM17-deficient mice possess the phenotype of mice with an EGF signaling defect (Buxbaum *et al.* 1998). ADAM10 can cleave Notch and ADAM10-deficient mice develop a loss of Notch

signaling phenotype (Hartmann *et al*. 2002). In addition, ADAM10 and ADAM17 were found to be directly responsible for the constitutive and protein kinase c-regulated processing of prions, respectively (Gouras *et al.* 2000; Vincent *et al.* 2001), whereas another ADAM member, ADAM9, acts as an upstream activator of ADAM10 during this process (Cisse *et al*. 2005).

β-secretase and β-cleavage

Aβ generation is initiated by β-cleavage at the ectodomain of APP, resulting in the generation of an sAPP-β domain and the membrane associated APP C-terminal fragment C99. The putative β-secretase, β-site APP cleaving enzyme 1 (BACE1), was first identified and characterized in 1999 (Sinha *et al.* 1999; Vassar *et al.* 1999; Yan *et al.* 1999; Hussain *et al.* 2000; Lin *et al.* 2000). BACE1 is a type I transmembrane aspartyl protease with its active site on the luminal side of the membrane. The originally identified full-length BACE1 has 501 amino acids (BACE1–501) and is predominantly expressed in perinuclear post-Golgi membranes, vesicular structures throughout the cytoplasm, as well as on the cell surface (Ehehalt *et al.* 2002). Several other minor transcripts of BACE1 (BACE1–476, 457 and 432) derived from alternative splicing were found later (Tanahashi and Tabira 2001), however their β-cleavage activity and subcellular localization are different from those of BACE1–501 (Tanahashi and Tabira 2001; Ehehalt *et al*. 2002). Knocking out the BACE1 gene prevents Aβ generation and completely abolishes Aβ pathology in mice expressing the Swedish mutation of human APP (Farzan *et al.* 2000; Cai *et al.* 2001; Luo *et al*. 2001; Roberds *et al.* 2001; Ohno *et al.* 2004; Laird *et al.* 2005). The expression level and activity of BACE1 were also found to be elevated in AD patients (Holsinger *et al.* 2002; Yang *et al.* 2003). However, there is no evidence linking BACE1 gene variants with familial AD (FAD) and the BACE1 gene variants do not affect BACE1's activity or APP processing/Aβ generation (Sjolander *et al.* 2010). More recently, BACE1 knockout mice have been found to exhibit hypomyelination and altered neurological behaviors, such as reduced grip strength and elevated pain sensitivity, probably because the physiological functions of other BACE1 substrates, such as neuregulin 1 and the voltage-gated sodium channel (Nav1) β2 subunit, are negatively affected in these mice (Laird *et al.* 2005; Hu *et al.* 2006; Willem *et al.* 2006; Gersbacher *et al.* 2010; Hitt *et al.* 2010).

BACE2 is a homolog of BACE1 (Acquati *et al.* 2000; Xin *et al.* 2000) and human BACE2 shares 71% homology and 45% identity with human BACE1. Similar to BACE1, BACE2 is predominantly localized in post-Golgi structures and on the cell surface (Ehehalt *et al.* 2002). Notably, Several splice variants of BACE2 were also identified and found to be expressed in several central nervous system subregions (Solans *et al.* 2000). However, the expression level of BACE2 is much lower in the brain than BACE1 and is mostly expressed in glial cells (Laird *et al.* 2005). In addition, BACE2 cleaves APP within the Aβ domain in a manner more similar to α-secretase than β-secretase (Farzan *et al.* 2000).

Cathepsin B was once suspected as a β-secretase candidate (Hook *et al.* 2005; Schechter and Ziv 2008). However, recent studies suggest that Cathepsin B can degrade Aβ into harmless fragments. It is therefore thought that Cathepsin B plays a role in the body's natural defense against AD (Mueller-Steiner *et al.* 2006).

γ-secretase and γ-cleavage

Both α-cleavage and β-cleavage generate short APP C-terminal fragments that are further processed by γ-secretase. Distinct from α-/β-secretases, γ-activity involves a large proteinase complex consisting of at least four major protein components (Presenilin1 or Presenilin2, PEN2, APH1 and Nicastrin) (Vetrivel *et al.* 2006).

Presenilins (PSs) were identified and cloned in the mid-1990s (Levy-Lahad *et al.* 1995; Sherrington *et al.* 1995). Genetic mutations of PSs are found in a large portion of familiar AD (FAD) cases, indicating its crucial role in AD. Although other proteins are required for the γ-secretase complex, PSs are believed to contain the actual protease activity (Wolfe *et al.* 1999; Wen *et al.* 2008; Ahn *et al.* 2010a). PSs are multi-transmembrane proteins and can be cleaved at the cytoplasmic loop between the 6^{th} and 7^{th} transmembrane regions to generate an N terminal and a C terminal fragment during post-translational maturation (Thinakaran *et al.* 1996). The two fragments interact with each other after the cleavage and they are both necessary for γ-secretase activity. Transgenic mice overexpressing PSs with FAD mutations show significantly increased Aβ42 levels, suggesting that PS mutations probably induce AD by producing more of the hydrophobic Aβ42 form (Duff *et al.* 1996; Xia *et al.* 2001).

Nicastrin, identified as a protein that interacts with PS in 2000 (Yu *et al.* 2000), is a type I membrane glycoprotein with a large ectodomain (Perrin *et al.* 2009). Nicastrin undergoes a glycosylation/maturation process that causes a conformation change in its ectodomain, which is crucial for the assembly and maturation of the γ-secretase complex and γ-activity (Shirotani *et al.* 2003; Chavez-Gutierrez *et al.* 2008). Mature nicastrin can bind to the ectodomain of APP CTFs derived through α-/β-secretase cleavage and may act as a substrate receptor of γ-secretase (Shirotani *et al.* 2003; Kaether *et al.* 2004; Shah *et al.* 2005).

PEN2 and APH1 are another two γ-secretase complex components that were originally identified as the enhancers of PSs (Francis *et al.* 2002). APH1 is a multiple transmembrane protein with seven transmembrane domains and a cytosolic C terminus (Fortna *et al.* 2004). APH1 interacts with immature nicastrin and PS to form a relatively stable pre-complex which is then translocated to the trans-Golgi from the ER/cis-Golgi for further maturation (Lee *et al.* 2002; Kimberly *et al.* 2003; Takasugi *et al.* 2003; Jankowsky *et al.* 2004). PEN2 is a hairpin-like protein with two transmembrane domains and with both ends in the lumen (Crystal *et al.* 2003; Takasugi *et al.* 2003). PEN2 is found to mediate the endoproteolysis of PS (Luo *et al.* 2003). Enhanced γ-secretase activity is also observed when PEN2 is exogenously expressed (Shiraishi *et al.* 2004).

The γ-secretase complex is assembled in sequential steps. Nicastrin and APH1 initially form a subcomplex (Shirotani *et al.* 2004) and then PS binds to the Nicastrin-APH1 subcomplex (Takasugi *et al.* 2003). The joining of PEN2 results in a conformation-dependent activation of γ-secretase (Kimberly *et al.* 2003; Takasugi *et al.* 2003). Nicastrin, PEN2, APH1 and PS interact with each other and also mutually modulate each other (Lee *et al.* 2002; Steiner *et al.* 2002; Pasternak *et al.* 2003; Kaether *et al.* 2004). Nicastrin ablation leads to decreased levels of APH1, PEN2 and PS1 fragments, accompanied by increased levels of immature full-length PS1 (Zhang *et al.* 2005). Downregulation of APH1, PEN2 or nicastrin also reduces the processing of PS and results in impaired γ-cleavage of APP and Notch (Francis *et al.* 2002). PS deficiency also results in decreased levels of PEN2 and APH1, as well as impaired glycosylation/maturation of Nicastrin (Zhang *et al.* 2005).

γ-secretase cleaves APP at multiple sites and in sequential steps to generate Aβ peptides of different lengths (Fig. 1). The majority of Aβ peptides produced are 40 amino acids long, however, peptides ranging from 38 to 43 amino acids are found *in vivo*. Besides the dominant γ-cleavage site at 40 and 42 residues, ζ-cleavage at 46 and ε-cleavage at 49 residues are also thought to be mediated by γ-secretase (Weidemann *et al.* 2002; Zhao *et al.* 2004; Raben *et al.* 2005; Sato *et al.* 2005). Accordingly, various AICDs (C50, C53, C57 and C59) can be generated during these multi-site cleavages executed by γ-secretase. However, all of the endogenous AICD forms are rarely detected, probably due to their very rapid degradation (Ag 2000; Lu *et al.* 2000; Sastre *et al.* 2001; Yu *et al.* 2001; Sato *et al.* 2003). Interestingly, as the substrate of γ-secretase, APP itself can regulate the intracellular

trafficking and cell surface delivery of PS1 (Kuzuya *et al.* 2007; Liu *et al.* 2009). In addition, APP has been found to possess a domain that negatively modulates γ-secretase activity in Aβ production by binding to an allosteric site within the γ-secretase complex (Kuzuya *et al.* 2007; Ahn *et al.* 2010b; Zhang and Xu 2010). These results reveal a novel mutual regulation between γ-secretase and its substrate.

In addition to cleaving APP, γ-secretase cleaves many other single transmembrane proteins within the transmembrane domain (Lee *et al.* 2002). One of the most important γ-secretase substrates, Notch, can release its intracellular domain (NICD) upon γ-cleavage. NICD is well-known as a signal molecule that transactivates a number of genes critical to development (Kopan *et al.* 1996; Schroeter *et al.* 1998). Mice with ablation of PS1, Nicastrin, or APH1A show Notch-deficient-like lethal phenotypes and neuronal tube formation defects (Shen *et al.* 1997; Donoviel *et al.* 1999; Li *et al.* 2003; Ma *et al.* 2005). Postnatal forebrain-specific inactivation of PS1 in APP transgenic mice, although preventing Aβ accumulation, failed to rescue contextual memory long-term. Conditional inactivation of γ-secretase components in the forebrain resulted in progressive memory impairment and age-related neurodegeneration (Dominguez *et al.* 2005; Saura *et al.* 2005; Serneels *et al.* 2009; Tabuchi *et al.* 2009).

Caspase-cleavage

In addition to cleavages involving secretases, APP can be cleaved by caspases independently at its C terminus (Asp664 of APP695), releasing a short tail containing the last 31 amino acids (C31) of APP and a fragment (Jcasp) from between the γ- and caspase-cleavage sites (Lu *et al.* 2000). Caspase-cleavages of APP are thought to be harmful since both C31 and the Jcasp fragment generated were found to be cytotoxic (Lu *et al.* 2003a). Transgenic mice with Swedish and Indiana mutations of APP show increased susceptibility to seizures, which can be abolished by a D664A mutation that disrupts caspase-cleavages (Ghosal *et al.* 2009). These results indicate that caspase-cleavages of APP contribute, at least in part, to the neurotoxicity of APP processing products.

Function of APP and its fragments

Full-length APP

Due to its highly similar structure to Notch, APP has been proposed to function as a cell surface receptor [reviewed in (Zheng and Koo 2011)]. Several studies have reported that certain ligands, including Aβ, F-spondin, Nogo-66, netrin-1 and BRI2, bind to the extracellular domain of APP, resulting in modulated APP processing and sequential downstream signals (Lorenzo *et al.* 2000; Lu *et al.* 2003b; Ho and Sudhof 2004; Park *et al.* 2006; Lourenco *et al.* 2009; Matsuda *et al.* 2009; Zheng and Koo 2011). However, the physiological functions of these interactions remain to be determined. Nevertheless, APP is more widely accepted as a protein contributing to cell adhesion via its extracellular domain. Studies have demonstrated that the E1 and E2 regions of APP can interact with extracellular matrix proteins (Small *et al.* 1999). Furthermore, the E1 and E2 regions of APP were found to interact with themselves, in parallel or anti-parallel, forming homo- (with APP) or hetero-dimers (with APLPs) (Wang and Ha 2004; Soba *et al.* 2005; Dahms *et al.* 2010). Recent studies also suggest APP/APLPs as synaptic adhesion molecules as silencing of APP led to defects in neuronal migration (Young-Pearse *et al.* 2007; Wang *et al.* 2009; Norstrom *et al.* 2010).

sAPP-α

The constitutively secreted sAPP-α has been found to be neuro-protective (Mattson *et al.* 1993; Furukawa *et al.* 1996; Han *et al.* 2005; Ma *et al.* 2009). sAPP-α is thought to promote

neurite outgrowth and synaptogenesis as well as cell adhesion (Mattson 1997; Gakhar Koppole 2008). Studies have found that sAPP-α is a growth factor (Herzog *et al.* 2004; Siemes *et al.* 2006) that regulates the proliferation of embryonic and adult neural stem cells (Ohsawa *et al.* 1999; Caille *et al.* 2004). *In vivo* studies have also shown that sAPP-α promotes learning and memory in animal models (Meziane *et al.* 1998; Taylor *et al.* 2008). sAPP-α alone is able to rescue most of the abnormalities of APP deficient mice (Ring *et al.* 2007), implying that most of the physiological functions of APP are conducted by its extracellular domain.

sAPP-β

Although there are only 17 amino acids difference between sAPP-β and sAPP-α, sAPP-β reportedly lacks most of the neuroprotective effects of sAPP-α (Furukawa *et al.* 1996). A recent study suggested that sAPP-β can be cleaved to generate an N-terminal fragment that is a ligand for death receptor 6, activating caspase-6 which further stimulates axonal pruning and neuronal cell death (Nikolaev *et al.* 2009).

Aβ

The physiological and pathological functions of Aβ have been extensively investigated due to its central role in AD. Studies have demonstrated that Aβ overproduction leads to neurotoxicity, neuronal tangle formation, synaptic damage and eventually neuron loss in the pathologically affected brain regions (Selkoe 1998; Shankar and Walsh 2009). Among the various Aβ peptides generated by the multiple-site cleavages of secretases, Aβ 42 has proved to be more hydrophobic and amyloidogenic than others (Burdick *et al.* 1992). Most mutations related to hereditary familiar AD either increase Aβ generation or the ratio of Aβ 42/ Aβ 40 (Borchelt *et al.* 1996; Scheuner *et al.* 1996). Studies also suggest that increased Aβ 42 levels probably provide the core for oligomerization, fibrillation and amyloid plaque generation (Jarrett *et al.* 1993; Iwatsubo *et al.* 1994).

Although excessive Aβ causes neurotoxicity, some studies have shown that Aβ40 protects neurons against Aβ42-induced neuronal damage and is required for the viability of central neurons (Plant *et al.* 2003; Zou *et al.* 2003). Moreover, two groups recently reported that low doses (picomolar) of Aβ can positively modulate synaptic plasticity and memory by increasing long-term potentiation (Morley *et al.* 2008; Puzzo *et al.* 2008), revealing a novel physiological function of Aβ under normal conditions.

AICD

Depending on the exact cleavage site of γ-secretase, AICD may have 59, 57, 53 or 50 residues. However, because AICD is quickly degraded after γ-cleavage, the biochemical features and physiological functions of AICD *in vivo* are difficult to study. So far, most of the information on AICD is deduced based on exogenous systems.

There are several conserved regions located on AICD: a YTSI (653–656 residues according to APP695) motif near the cell membrane, a VTPEER (667–762 residues) helix capping box and a YENPTY (682–687 residues) domain which mediates the interaction between APP/AICD and phosphotyrosine binding (PTB) domain containing proteins. Many AICD binding proteins have been identified. Some of the proteins, including KLC, Fe65, Shc, JIP, Numb, X11, Clathrin and mDab1, were found to share one or several common PTB domains that specifically interact with the Asn-Pro-X-Tyr amino acid sequence present in the YENPTY motif of AICD (Borg *et al.* 1996; Brassler *et al.* 1996; M. McLoughlin and Cj Miller 1996; Howell *et al.* 1999; Salcini *et al.* 1999; Kamal *et al.* 2000; Matsuda *et al.* 2001; Weggen *et al.* 2001; Roncarati *et al.* 2002; Tarr *et al.* 2002b; Tarr *et al.* 2002a; Inomata *et al.* 2003; Matsuda *et al.* 2003). Other proteins, such as PAT1, SET and 14-3-3γ, are believed to bind

to the YTSI or VTPEER motif of AICD (Zheng *et al.* 1998; Madeira *et al.* 2005; Sumioka *et al.* 2005). AICD, therefore, may have different functions when interacting with its' various binding partners.

AICD also contains three phosphorylation sites, including two threonine residues at 654 and 668 and a serine residue at 665. AICD has been found to be phosphorylated by PKC, calcium-calmodulin dependent-kinase II, GSK3-β, Cdk5 and JNK at the Ser/Thr sites mentioned above. Such phosphorylation may affect APP processing or the binding of AICD-interacting proteins, thus affecting the function of AICD (Gandy *et al.* 1988; Iwatsubo *et al.* 1994; Iijima *et al.* 2000; Inomata *et al.* 2003).

Since the generation of AICD is very similar to that of many other signaling molecules, such as NICD, which is also generated by γ-cleavage and can mediate the transcription of genes important for development, AICD may function in a similar fashion. Indeed, a role for AICD in gene transactivation is supported by several studies. The most widely accepted mechanism is that AICD, together with Fe65 and Tip60, forms a transcriptionally-active complex. Fe65 is one of the most well studied proteins that bind to the YENPTY motif of AICD. Tip60, a histone acetyltransferase, is a component of a larger nuclear complex with DNA binding, ATPase and DNA helicase activities (Ikura *et al.* 2000). Although Tip60 does not bind to AICD directly, an indirect interaction between AICD and Tip60 is mediated by Fe65. Upon forming this complex, AICD is stabilized and can be translocated into the nucleus to regulate expression of genes such as KAI1, Neprilysin, LRP1, p53, GSK-3β and EGFR (Baek *et al.* 2002; Kim *et al.* 2003; Cao and Sudhof 2004; Pardossi-Piquard *et al.* 2005; Alves da Costa *et al.* 2006; Liu *et al.* 2007; Zhang *et al.* 2007). Another transactivating complex consisting of AICD, Fe65 and CP2/LSF/LBP1 has also been reported to induce the expression of GSK3-β (Kim *et al.* 2003). Although the transactivation effect of AICD has been observed by different research groups, the model of how AICD functions is still controversial (Cao and Sudhof 2004; Hass and Yankner 2005; Nakaya and Suzuki 2006). It was originally widely accepted that translocating into the nucleus was necessary for AICD to activate gene expression. However, some studies have suggested that an AICD mediated conformational change in Fe65 is sufficient and that the nuclear translocation of AICD is not required (Cao and Sudhof 2004; Hass and Yankner 2005). Another study has suggested that the nuclear translocation of AICD is independent of Fe65 and is a result of its phosphorylation at T668 (Nakaya and Suzuki 2006). More investigation is required to further elucidate the mechanism.

As an adaptor protein involved in protein sorting and trafficking, X11 has been suggested as affecting APP trafficking/metabolism by interacting with AICD, leading to reduced Aβ production. X11 has also been found to suppress the transactivation of AICD, possibly by competing with AICD for the recruitment of Fe65, as they share the same binding motif (Biederer *et al.* 2002).

Many studies have documented that AICD is cytotoxic and that overexpressing different AICDs (C31, C57, C59) in Hela, H4, N2a or PC12 cell lines, as well as neuronal cell lines, induces cell death (Lu *et al.* 2000). AICDs lacking the NPTY motif that mediates the interaction between AICD and other proteins failed to induce apoptosis, suggesting the functional involvement of an AICD-binding protein (Xu *et al.* 2006). A Tip60 loss-of-function mutation makes Hela cells more resistant to apoptosis (Ikura *et al.* 2000). These results indicate that the cytotoxicity of AICD may be mediated by its interacting proteins. For example, JIP is the scaffolding protein of the JNK pathway kinase and is involved in various cell events including neuronal apoptosis and axonal transporting. By binding to AICD, JIP mediates APP/AICD phosphorylation at Thr668, thus modulating APP

trafficking, maturation and processing. Additionally, there is evidence suggesting that the cell death triggered by AICD is partially mediated by JIP (Taru *et al.* 2002).

In addition, AICD-induced cytotoxicity may be mediated by its regulation targets (Kim *et al.* 2003; Alves da Costa *et al.* 2006; Vetrivel *et al.* 2006). For example, P53 expression, as well as p53-mediated apoptosis, can be enhanced by AICD (Alves da Costa *et al.* 2006; Ozaki *et al.* 2006). Another AICD target gene, GSK3-β, may also contribute to AICD-related cytotoxicity by upregulating tau hyperphosphorylation. GSK-3β activation and CRMP-2 phosphorylation, along with downstream tau hyper-phosphorylation/aggregation, neurodegeneration and memory loss, are observed in an AICD C59 transgenic mouse line in which Fe65 is co-expressed (Ryan and Pimplikar 2005; Ghosal *et al.* 2009). However, another group found only increased neuronal sensitivity to toxic and apoptotic stimuli in mice overexpressing AICD either alone or with Fe65 (Giliberto *et al.* 2008).

On the other hand, C31, a short form of AICD generated by caspase cleavage, has been reported to directly activate caspase-3 in the tumor cell death process (Lu *et al.* 2000; Bertrand *et al.* 2001; Nishimura *et al.* 2002; Madeira *et al.* 2005). C31 also appears to induce a caspase-independent toxicity by selectively increasing Aβ42 (Dumanchin-Njock *et al.* 2001). A D664A mutation in AICD, blocking caspase cleavage, abolished the synaptic loss, axonal defects and behavioral changes found in PDAPP(D664A) mice (Galvan *et al.* 2006). APP binding protein 1 (APBP1) reportedly interacts with AICD and activates the neddylation pathway (Chen 2004), further downregulating the level of β-catenin and potentially resulting in apoptosis. In addition, cellular Ca^{2+} homeostasis appears to be modulated by AICD (Hamid *et al.* 2007).

Conclusion

As a crucial protein in AD, APP is multifunctional and can be post-translationally processed via different pathways. The physiological and pathological functions of APP are closely related to the processing of APP, which may suggest therapeutic treatments for AD. In this review, we have summarized the current knowledge of APP metabolism. Further understanding of APP processing and the patho/physiological functions of various APP metabolites will be important for the development of an AD treatment.

Abbreviations used

Aβ	β-amyloid
AD	Alzheimer's disease
ADAM	a disintegrin and metalloproteinase
AICD	APP intracellular domain
APLP1	APP-like protein 1
APLP2	APP-like protein 2
APP	β–amyloid precursor protein
BACE1	β-site APP cleaving enzyme 1
cDNA	complementary DNA
EGF	epidermal growth factor
FAD	familiar Alzheimer's disease
KPI	Kunitz protease inhibitor

NICD	Notch intracellular domain
PS	presenilin
PTB	phosphotyrosine binding

Acknowledgments

This work was supported in part by National Institutes of Health grants (R01AG021173, R01NS046673, R01AG030197 and R03AG034366 to H.X.), and grants from the Alzheimer's Association (to H.X. and Y.-w.Z.), the American Health Assistance Foundation (to H.X.), National Natural Science Foundation of China (30973150 to Y.-w.Z.), the 973 Prophase Project (2010CB535004 to Y.-w.Z.), and Natural Science Funds for Distinguished Young Scholar of Fujian Province (2009J06022 to Y.-w.Z.). Y.-w.Z. is supported by the Program for New Century Excellent Talents in Universities (NCET), the Fundamental Research Funds for the Central Universities, and Fok Ying Tung Education Foundation.

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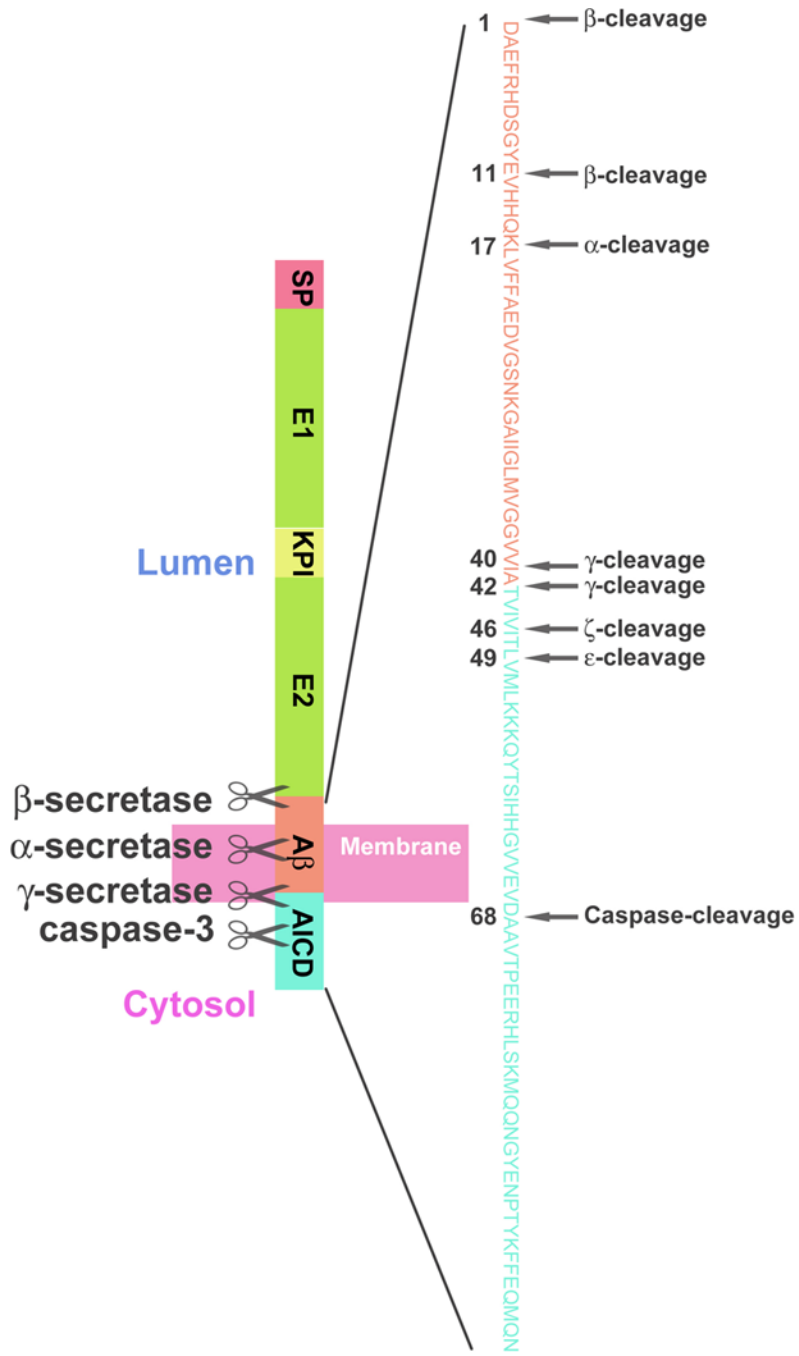

Fig. 1.
Proteolytic processing of APP.