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The multifaceted nature of amyloid precursor protein and its proteolytic fragments: friends and foes

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Abstract

The amyloid precursor protein (APP) has occupied a central position in Alzheimer's disease (AD) pathophysiology, in large part due to the seminal role of amyloid-β peptide (Aβ), a proteolytic fragment derived from APP. Although the contribution of Aβ to AD pathogenesis is accepted by many in the research community, recent studies have unveiled a more complicated picture of APP's involvement in neurodegeneration in that other APP-derived fragments have been shown to exert pathological influences on neuronal function. However, not all APP-derived peptides are neurotoxic, and some even harbor neuroprotective effects. In this review, we will explore this complex picture by first discussing the pleiotropic effects of the major APP-derived peptides cleaved by multiple proteases, including soluble APP peptides (sAPPα, sAPPβ), various C- and N-terminal fragments, p3, and APP intracellular domain fragments. In addition, we will highlight two interesting sequences within APP that likely contribute to this duality in APP function. First, it has been found that caspase-mediated cleavage of APP in the cytosolic region may release a cytotoxic peptide, C31, which plays a role in synapse loss and neuronal death. Second, recent studies have implicated the –YENPTY– motif in the cytoplasmic region as a domain that modulates several APP activities through phosphorylation and dephosphorylation of the first tyrosine residue. Thus, this review summarizes the current understanding of various APP proteolytic products and the interplay among them to gain deeper insights into the possible mechanisms underlying neurodegeneration and AD pathophysiology.

Keywords

Alzheimer's disease (AD); Amyloid precursor protein (APP); Amyloid-β peptide (Aβ); Caspases; C31; YENPTY

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Introduction

Alzheimer's disease (AD) is the most common age-associated dementia. The pathological hallmarks of AD are senile plaques consisting of extracellular accumulation of amyloid fibrils and intraneuronal formation of neurofibrillary tangles consisting of aggregates of hyperphosphorylated tau protein. While these lesions have been known for over a century since the initial description in 1907, the question of "what causes Alzheimer's disease?" remains elusive. In the rare familial forms of AD, the causative mutations lie within the amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) genes. The vast majority of AD cases, however, are sporadic in origin with contribution by a number of genes that increase the susceptibility to disease. In addition, multiple factors, such as environment and nutrition, have been proposed to contribute to the risk of developing this complex disease. Because of the characteristic lesions in the brain, it is natural to hypothesize that senile plaques and neurofibrillary tangles play key pathogenic roles in the disease process. Indeed, the prevailing hypothesis that has generally guided the field is the so-called "amyloid cascade hypothesis," first coined by Hardy and Higgins [46] in the early 1990s. This hypothesis posits that abnormal aggregation of amyloid-β peptide (Aβ) in brain initiates the cascade of events that results in pathological changes, neurodegeneration and cognitive decline. However, most studies have shown that the number or density of plaques in brain does not correlate with the degree of dementia, and that plaque formation occurs in healthy brains even without signs of cognitive decline. This inconsistency has recently been explained by invoking soluble Aβ species rather than the highly aggregated Aβ fibrils as the toxic species that damage synapses and injure neurons [67, 121]. As such, the amyloid hypothesis has been modified to embody the concept that soluble Aβ oligomers are the toxic species, and that they are present before Aβ peptides are aggregated and deposited as amyloid plaques in brain. In this scenario, these toxic oligomers derived from APP are the main culprits underlying synaptic dysfunctions and are responsible for initiating cognitive deficits before the characteristic lesions are manifested in brain.

Given our still incomplete understanding of AD pathophysiology and the well-known but not universally accepted amyloid cascade hypothesis, there is, not surprisingly, continued interest in other potential disease mechanisms, especially after negative outcomes from a number of clinical trials testing anti-amyloid therapeutics for AD treatment. In this context, it is understandable that for example, tau-focused hypotheses have recently gained momentum in light of mutations in the *tau* gene associated with frontotemporal dementia and evidence that tau is intricately involved in amyloid pathology. Indeed, it has been known for some time that tau pathology correlates better with cognitive impairments observed in AD patients than amyloid pathology [126]. While the influence of tau and other proposed mechanisms in AD pathophysiology have their individual merits, they will not be discussed in this review; instead, we will focus on the proteolytic products of APP that might contribute to AD pathogenesis. Generation of Aβ peptide requires two sequential cleavages by β- and γ-secretases. However, these two secretases, together with α-secretase, constitutively generate many other additional fragments, some containing while others excluding the Aβ peptide. Interestingly, these APP-derived peptides have been shown to exhibit both neuroprotective and neurotoxic properties. Whether APP proteolysis generates

fragments that demonstrate Aβ-independent activities and contribute to AD pathogenesis is still an intriguing question that has not been adequately addressed. In this review, we will explore the major APP proteolytic peptides and examine their trophic and/or toxic effects identified in various in vitro and in vivo systems, as well as how they may contribute to AD pathophysiology. Although Aβ is a major, if not the major, peptide derived from APP, we have chosen to focus primarily on the non-Aβ polypeptides as many indepth and insightful reviews have been published on Aβ. In so doing, we hope this will stimulate the reader to consider APP proteolytic products other than Aβ when reflecting on the mechanisms underlying this complex disorder.

APP processing

Before exploring the major APP-derived peptides, it is necessary to provide a brief overview of the proteolytic processing of APP. APP, encoded by a gene located on chromosome 21, is a type I integral membrane protein with different isoforms generated through alternative splicing. The APP695 isoform (so designated because of 695 encoded amino acid residues) is primarily expressed in neurons while the two longer APP751 and APP770 isoforms are expressed in other tissues and cell types. Additional isoforms, as short as 365 amino acids, have also been identified and their physiological roles remain unclear. The main difference between APP695 and the longer isoforms is the lack of a Kunitz-type serine protease inhibitor (KPI) sequence in the extracellular domain. APP is part of a larger gene family that is evolutionarily conserved across different species (APL-1 in *C. elegans*, APPL in *Drosophila*, APPa, APPb in zebrafish, and all three members, APP, APLP1, APLP2 in mice), with the most sequence homology in the N- and C-termini. The *APP* gene is located on the long arm of human chromosome 21 and encompasses 18 exons [146]. As the expression of the APP695 isoform is neuron specific, the numbering scheme of APP residues used in this review is based on the APP695 isoform.

Amyloid precursor protein is constitutively cleaved by α-, β-, and γ-secretases during APP maturation and processing (Fig. 1). There is no single α-secretase, but rather several members of the ADAM (a disintegrin and metalloprotease) family, particularly ADAM9, ADAM10, and ADAM17—also known as TACE (tumor necrosis factor α-converting enzyme)—appear to fulfill this function. Cleavage of APP by α-secretase releases the soluble ectodomain of APP, termed sAPPα, and a membrane-tethered intracellular C-terminal fragment, called CTFα or C83. Cleavage by β-secretase yields a slightly shorter soluble APPβ fragment (sAPPβ) and a correspondingly longer CTFβ or C99 (Fig. 1a) [146]. Unlike α-secretases, β-secretase is a single transmembrane aspartyl protease termed BACE1 (β-site APP cleaving enzyme, also known as Asp-2 and memapsin-2). The cleavage by BACE1 between residues 671 and 672 generates the N-terminus of Aβ. But there is a second β-secretase cleavage site (β′) that is 10 amino acids towards the C-terminus from the β site, yielding CTF89 [146]. Lastly, γ-secretase—a high molecular weight complex that consists of presenilin (PS), nicastrin, anterior pharynx defective (APH1) and presenilin enhancer (PEN2)—cleaves APP C-terminal fragments (CTFs) such as C83, C99 within the transmembrane domain to release the Aβ peptides. Notably, γ-secretase is active on APP only following the antecedent cleavage by α- or β-secretase. The products of γ-secretase cleavage of C83 are a 3-kDa peptide, termed p3, and an APP intracellular domain (AICD),

while γ-secretase cleavage of C99 yields the infamous Aβ peptide and an identical AICD fragment (Fig. 1a). Further cleavage of AICD fragments by caspases or caspase-like proteases at Asp664 (D664) results in 2 additional fragments: Jcasp (from the N-terminus to D664) and C31 (from the caspase cleavage site to the C-terminus of APP) (Fig. 1b) [17, 75]. However, cleavage at position 664 does not appear to require antecedent proteolysis of APP. Besides cleavage by α-, β-, and γ-secretases, several studies have identified other N-terminal fragments (NTFs) of APP in human and rodent tissues that are generated by unknown proteases [28, 102, 136].

APP proteolytic fragments

Full-length APP

Besides the reported biological properties such as facilitating cell adhesion, acting as a cell surface receptor, regulating synapse formation and cell division, APP has been found to exhibit both neurotoxic and neurotrophic protective effects [146]. It is difficult to pinpoint the properties of full-length APP because over-expression or down-regulation of APP in various cell systems will invariably alter the generation of the many proteolytic products, thus rendering it virtually impossible to isolate the precise physiological role of uncleaved APP, if any. Further, the potential compensatory effects of APLP1 and APLP2, when APP is down-regulated or absent, are not easily measured.

With these caveats in mind, APP has been reported or inferred to demonstrate neuroprotective properties. Initially, it was shown that PC12 pheochromocytoma cells transfected with full-length APP did not induce degeneration [143], and that down-regulation of APP using antisense oligonucleotides was found to inhibit neurite outgrowth in primary cultured neurons [2]. Further, expression of APP in B103 cells, a cell line that does not produce APP endogenously, was found to protect those cells from Aβ and glutamate toxicity [119]. Consistent with the previous findings, transgenic mice over-expressing human APP751 (hAPP751) or hAPP695 (i.e., with or without the Kunitz protease inhibitor domain, respectively) showed an increase in the number of synaptophysin immunoreactive presynaptic terminals in the frontal cortex. Further, these mice did not exhibit either neurodegeneration or amyloid deposits over the course of 24 months [86].

In vitro studies demonstrated that full-length wild-type human APP (hAPP) cDNA transfected into murine embryonic carcinoma P19 cells showed severe degeneration with intracellular accumulation of large amounts of truncated APP derivatives [145]. Similar in vitro results were found in the neuroblastoma cell line NB-1 transfected with APP cDNA [78], embryonic carcinoma NT2 cells and rat hippocampal neurons infected with recombinant adenovirus vector expressing hAPP695 [135], as well as the SK-N-MC human neuroblastoma cell line HTB10 transfected with APP695 [106]. These in vitro findings were corroborated by in vivo data showing degeneration caused by over-expression of the same adenovirus vector of wild-type APP695 in rat hippocampus [96]. In all these studies, severe neurodegeneration with apoptotic features such as membrane blebbing, DNA fragmentation, and caspase-3 activation were observed [78, 96, 135, 145]. However, the same caveats stated earlier also apply to these findings, in that the observed toxicity could be due to one or

more APP proteolytic fragments, not just APP itself. Further, these studies employed transfection systems where APP was expressed at supraphysiological levels.

Perhaps the best evidence that over-expression of APP is detrimental comes from APP gene triplication due to trisomy 21 in humans and trisomy 16 in mice where the APP gene is located, respectively. Of interest are the observations that in humans, individuals with trisomy 21 invariably develop AD pathology beyond the third decade of life. In support of the notion that this is due to increased gene dosage, an individual with partial trisomy 21 but without triplication of the APP or surrounding genes did not develop AD changes in the seventh decade of life [104]. Further, rare families with triplication of the APP gene locus without Down's syndrome (DS) demonstrated AD pathology and Aβ deposits in the cerebral blood vessels (congophilic angiopathy) [110]. Finally, endosomal abnormalities are seen in AD, DS and in segmental trisomy 16 in mice, the latter where the APP gene is present in three copies, e.g., Ts65Dn and 1YeY mouse lines [23]. Remarkably, both endosomal alterations and disruption of retrograde NGF signaling were restored in these segmental trisomic 16 mice when only the APP gene dosage was reduced back to the diploid state by crossing the Ts65Dn to an APP knockout mouse line [115]. These results showed convincingly that excess APP gene dosage, in three copies, resulted in neuronal dysfunction and exhibited features seen in AD. However, it is still unclear as to how these alterations are mediated or which domain(s) of APP mediate these neurotoxic activities.

Aβ

After cleavage by β-secretase, C99 is proteolyzed by γ-secretase to release the 4-kDa Aβ peptide and AICD (Fig. 1). Again, because Aβ has been the subject of many thorough reviews, only a few highlights will be discussed here.

Aβ is constitutively produced in vivo in brain and, in lesser amounts, outside of the brain. Given its central role in AD pathogenesis, it is perhaps surprising that Aβ has been shown to exhibit many other properties in addition to neurotoxicity. For example, Aβ may function as a signaling molecule, a transcriptional factor, a cholesterol transport regulator, and an antimicrobial agent. However, studying Aβ has proven to be complicated in part because of the many conformations that Aβ can adopt, including monomers, oligomers, protofibrils, and fibrils [138]. Indeed, the pleiotropic nature of Aβ can be partially explained by different preparations used in the studies, for example: $A\beta_{1–40}$, $A\beta_{1–42}$, $A\beta_{25–35}$, synthetic vs. naturally derived, monomers vs. oligomers or fibrils, not to mention variations in concentration, incubation time, as well as experimental systems.

Under basal conditions, ~90 % of Aβ produced is Aβ40, with Aβ42 consisting of less than 10 %. While there is an emphasis on Aβ40 and Aβ42 in the literature, Aβ peptides are heterogeneous with both N- and C-terminally truncated species as well as longer species, such as Aβ43, the latter being a putatively pathogenic species [122]. The majority of Aβ peptides are cleaved by BACE1 between Met(-1) and Asp1 to produce $A\beta_{1–x}$, with a small percentage of cleavages by other enzymes (Neprilysin, plasmin, aminopeptidase A, meprin-β, myelin basic protein, and angiotensin-converting enzyme) to begin at Ala2, Glu3, Phe4, Arg5, His6, Asp7, Ser8, Gly9, Tyr10, and Glu11 [14]. Perhaps due in part to the variability in conditions mentioned above, results from studies aiming to elucidate the biological effects

of Aβ in brains have been conflicting, with reports suggesting both neurotoxic and neurotrophic properties, perhaps depending on the form of Aβ used. It is worth noting that post-translational modification of Aβ, such as phosphorylation, nitration, and pyroglutamate conversion, appears to contribute significantly to seed the aggregation of Aβ peptide, leading to its accumulation and deposition in plaques in brain [65, 66, 118].

In general, Aβ40 is less toxic than Aβ42, and has the ability to inhibit Aβ42 oligomerization [89]. Indeed, early studies appeared to emphasize the trophic properties as addition of synthetic Aβ28 and Aβ42 (in the micromolar range) to culture medium resulted in a dose-dependent effect on the survival and neurite outgrowth of rat hippocampal neuronal cultures [141]. Similarly, Aβ40 was found to promote neurogenesis in neural progenitor cells [25], prevent toxicity induced by α-secretase inhibitor, but could be both toxic and trophic depending on the dosage used [144]. In cultured rat dorsal root ganglion explants, Aβ40 can interact with extracellular matrix components, such as laminin and fibronectin, to promote extensive neurite proliferation [64].

Aβ42 is believed to be more toxic than Aβ40 because of its tendency to aggregate to form fibrils [138]. Although earlier studies have focused on highly aggregated Aβ peptides, recent studies have emphasized the potentially seminal role played by soluble low-n Aβ oligomers [87, 121]. For example, rodent hippocampal neurons treated with Aβ oligomers isolated directly from AD brain inhibited longer-term potentiation (LTP), enhanced long-term depression (LTD), and reduced synaptic spine density [121]. Different groups have studied the effects of soluble Aβ oligomers on the nervous system using synthetic [67] or cell-derived Aβ peptides [120], cell culture systems over-expressing Aβ [78], or transgenic animals engineered to over-express APP in brain [87]. The general belief is that soluble Aβ42 oligomers induce a variety of neurotoxic effects, including a reduction in synaptic density, perturb synaptic transmission, inhibit hippocampal LTP, and impair cognitive functions. However, not all forms of Aβ42 peptides are toxic. In fact, Aβ42 monomers were found to be neuroprotective, especially in low picomolar concentrations [120].

Another interesting aspect of Aβ biology is the recent description of activity-dependent release of Aβ in vitro and in vivo [26, 58]. Because of the proposed neuronal toxicity of Aβ, this activity-related generation of Aβ suggests a negative feedback mechanism, whereby Aβ released following neuronal activity may subsequently depress synaptic activity [58]. Long-term inhibition of Aβ degradation mimics APP over-expression, which also leads to synaptic loss [1]. Further, deafferentation of the fibers from either the whiskers or the perforant pathway in rodents resulted in reduced amyloid deposition in the terminal projections of these two projections in the barrel cortex or dentate gyrus of the hippocampus, respectively, as predicted by the activity-dependent mode of Aβ generation [16, 130]. Recently, an interesting correlation has been demonstrated from neuroimaging studies where the sites of Aβ deposition in brain are highest in the brain regions of the so-called “default mode network”, where neurons in this network are preferentially active when the individual is not focused on the external environment [21].

p3

Subsequent to α-secretase cleavage, C83, like C99, is cleaved by γ-secretase within the transmembrane domain) to yield a 3-kDa peptide (p3) and the APP intracellular domain, AICD (Fig. 1) [143]. This 3-kDa peptide ($A\beta_{17–42}$) was first isolated and characterized from diffuse amyloid deposits in AD brains [42], thus confirming these APP processing steps in vivo. Moreover, p3 has been found in plaques, and is also a major constituent of cerebellar pre-amyloid deposits in Down's syndrome brains [53, 68, 132]. Yankner et al. [143] first described the neurotoxic effects of synthetic Aβ peptide fragment containing residues 25–35 at micromolar concentrations. Because p3 contains the sequences critical for neurotoxicity, it was reasonable to hypothesize that p3 would exhibit a certain degree of toxicity. Studies have shown that p3 was able to induce apoptosis in cultured cells, albeit at a lower potency than Aβ42 [139]. Further, the p3 fragment, along with Aβ peptide, was found to promote inflammatory responses in various cell types (differentiated human monocyte line THP-1, microglia cell line MG7, murine and human astrocyte lines D30 and U373) by producing proinflammatory cytokines interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and chemokine MCP-1 to varying degrees [128]. In sum, though not a focus of much investigation, p3 might harbor neurotoxic activities. However, because it does not contain the fully intact Aβ peptide, it has been generally assumed that p3 peptide may be relatively innocuous, a notion that may be incorrect [29].

sAPPα

Cleavage of APP by α-secretase within the Aβ peptide between amino acids 16 and 17 concomitantly releases the large ectodomain sAPPα and the membrane-anchored APP C-terminal fragments (CTFα or C83) (Fig. 1a). This cleavage event can be enhanced by a variety of stimuli, such as protein kinase C (PKC) or cholinergic activation, suggesting that this cleavage is regulated by cellular activity [3].

A number of studies dating back more than 20 years have suggested a trophic role for αAPPs. Lower levels of sAPPα have been found in the cerebrospinal fluid of AD patients compared to healthy subjects [69]. Low levels of sAPPα have also been found to correlate with impaired spatial memory performance in rats [5] and in AD patients [4], suggesting an important neurotrophic role of sAPPα in facilitating normal physiological functions. Initially, the secreted portion of APP was found to promote fibroblast growth [114]. Since then, ample in vitro and in vivo evidence have suggested that sAPPα peptides contribute favorably to normal memory functions and neuronal survival [6, 83, 108, 114]. The notable neurotrophic effects of sAPPα include its ability to attenuate the normal rate of cell death in rat primary cortical neurons, to prevent cell death in cultured neurons or neural cells induced by hypoglycemia, glutamate, Aβ, epoxomicin, and UV irradiation, and to promote rat neural stem cell proliferation [24]. Exogenous administration of sAPP or small peptides encoding the trophic domain of sAPP in mice, rats, and chicks increased synaptic density in vivo, and enhanced memory performance in those animals [83, 85]. Intracerebroventricular injection of an antibody specifically against sAPPα ($APP_{598–611}$) diminished LTP by approximately 50 %, while infusion of recombinant sAPPα increased LTP induction and facilitated in vitro tetanically evoked NMDAR-mediated currents, as well as increased spatial memory

performance as reported in other studies [131]. These findings suggested that reduced levels of sAPPα could contribute to neuronal dysfunction or degeneration.

Within the large sAPPα fragment, several domains have been identified to promote neurite outgrowth: $APP_{96–110}$, $APP_{319–335}$, and $APP_{591–612}$ with the first sequence being mapped as a potential heparin-binding site [123]. Within the $APP_{319–335}$ region, Jin et al. [56] identified a five aminoacid sequence—RERMS ($APP_{328–332}$)—that exhibited neurotrophic properties in B103 cells. More intriguingly, $APP_{591–612}$ contains the sequence of $Aβ_{1–16}$ that exists in sAPPα but not in sAPPβ. As discussed later, it is the lack of this sequence that makes sAPPβ 100 times less potent than sAPPα, solidifying the important role of the last 16 amino acids of sAPPα for its neurotrophic properties [33]. However, full-length sAPPα was less neurotrophic than shorter fragments ($APP_{444–612}$ and $APP_{591–610}$) for unclear reasons. On the other hand, Aβ peptide itself contains the same 16-amino acid sequence, yet its effects have been claimed to be both toxic and trophic. Thus, this duality in Aβ is particularly intriguing. Because Aβ toxicity is related to its oligomerization state, it may be the presence of the aggregation activity in the latter half of Aβ that leads to this switch from trophic to toxic.

Consistent with the in vitro studies, introduction of sAPPα into brain has beneficial properties, for example, intracerebroventricular administration of sAPPα following traumatic injury significantly reduced cell and axonal death and improved motor outcome in rats [133]. Similarly, intracerebroventricular injection of sAPP protects CA1 hippocampal neurons against ischemic injury [124]. To further investigate the role of sAPPα in vivo, Ring et al. [107] engineered a transgenic mouse line that expressed only sAPPα in an APP-null background (sAPPα-KI mice) by gene targeting. Compared to APP-deficient mice, sAPPα-KI mouse did not demonstrate reductions in brain and body weight, deficits in grip strength, alterations in circadian locomotor activity, or impairments in learning and memory or LTP as seen in the APP knockout mice. This lack of negative phenotypes was interpreted to imply that these deficits were due to a lack of sAPPα activity in the APP-deficient parental mouse line, although the lack of neurotoxic effects of other APP derivatives cannot be excluded [107]. Moreover, the subventricular zone of the lateral ventricle has been found to be a major sAPP-binding site and infusion of sAPP into the lateral ventricle of adult mice increased the number of epidermal growth factor (EGF)-responsive progenitor cells, suggesting that sAPP might play an important role in promoting stem cell proliferation [147]. Lastly, while a loss of the APP ortholog in *C. elegans*, *apl-1*, leads to larval lethality, such a lethal effect can be rescued by expression of only the extracellular domain of APL-1, again suggesting that sAPPα represents the primary function of APP, at least in the nematode's developmental processes [49].

Paradoxically, while the trophic properties of sAPPα are favorable under normal physiological conditions, an over-abundance of sAPPα could drive the system towards tumorigenesis [24]. Soluble APPα has been found to be secreted in copious amount in various human cancer cell lines [51]. It has also been linked to promoting abnormal cell growth in pancreatic cancer cells via various MAP kinase or protein kinase C signaling pathways [44], as well as in a number of solid cancers [129]. Moreover, APP has been shown to be a target for androgen-mediated growth in prostate cancer [129]. These findings

suggested that APP, or more specifically sAPPα, could behave as tumorigenic molecules when dysregulated and perhaps even represent new targets for therapy.

In summary, the preceding findings suggest that sAPPα represents the primary physiological function of APP. It is also the most neurally beneficial proteolytic product derived from APP processing under normal physiological conditions. However, aberrant sAPPα production may tilt the cells toward unregulated growth. Though the neurotrophic properties have been mapped to multiple domains, the mechanisms underlying these trophic activities are still largely unknown.

sAPPβ

Following cleavage by β-secretase (BACE1), two APP fragments are generated: sAPPβ and the C-terminal fragment of 99 amino acids, also known as C99 (Fig. 1a). A second less prominent BACE1 cleavage site 10 amino acids to the C-terminus of APP (β′) allows the generation of C89, but not much is known about this CTFβ′. In some of the soluble APP studies described above, the experiments were conducted with both sAPPα and sAPPβ. Hence, the neurotrophic effects of sAPPα can be extended to include sAPPβ. However, compared to sAPPα, sAPPβ has been shown to be significantly less active. Even if sAPPβ exhibits neuroprotective effects, its potency is about 100-fold lower than that of sAPPα in protecting hippocampal neurons against excitotoxicity, Aβ-induced toxicity, and glucose deprivation [33], perhaps because it lacks a major neurotrophic domain that lies within the first 16 amino acids of Aβ as discussed earlier. Consistent with this notion, application of sAPPβ to acute brain slices 10 min before applying high-frequency stimulation resulted in no changes in LTP, unlike sAPPα described above [131].

Despite their prominent trophic properties, one additional interesting hallmark of both sAPPα and sAPPβ is their ability to robustly stimulate microglia activation through MAP kinase signaling pathways [8]. Treatment of rat microglial cells with sAPPα enhanced active ERKs, p38 kinase, and JNKs in addition to an increase in NFκB activity [12]. Those transcriptional factors are the precursors to a whole host of other downstream proinflammatory and neurotoxic products such as iNOS, IL-1β, and reactive oxygen species [8]. Therefore, it was not unexpected to find that secreted sAPPα- and sAPPβ-stimulated microglia were toxic to neuronal cultures [12]. Further, sAPPβ can be subsequently proteolyzed to generate a cytotoxic derivative that interacts with the DR6 receptor (see below). Thus, in the context of these trophic and toxic properties attributed to both sAPPα and sAPPβ, the regulated cleavage and release of these soluble fragments described above possibly gains further physiological significance. However, it is unclear what processes trigger the system to switch between trophic to toxic tendencies, and whether there is a dominant activity in vivo.

CTFα (C83)

While the neuroprotective effect of sAPPα is well established, little is known about the properties of C83, the complementary fragment generated along with sAPPα after α-secretase cleavage (Fig. 1a). This fragment lacks the trophic domain embedded in the first 16 amino acids of C99 or CTFβ, thus it might be predicted to be toxic especially given the

putative toxic properties of the intact cytoplasmic domain (see below). On the other hand, perhaps C83 is beneficial by virtue of the fact that cleavage by α-secretase would reduce the levels of full-length and toxic Aβ peptides. Or in other words, it is indirectly promoting survival by lowering the levels of C99 to the more "benign" C83 [54], especially because C99 is a better substrate for γ-secretase than C83 [100]. Moreover, as described previously, α-secretase activity is promoted by activation of G protein-coupled receptors, PKC, or NMDA receptors [48], thus suggesting this cleavage event is highly regulated. In sum, α-secretase processing steers the system away from the amyloidogenic pathway and this is reflected by corresponding changes in CTFα (reviewed in [103]).

CTFβs

Together with Aβ, the APP CTFs were shown to be neurotoxic quite early on in studies of APP biology. In vitro cell culture studies revealed that CTFβs containing the last 99–105 amino acids (CT99 to CT105, depending on the cDNA constructs used) were found to be selectively neurotoxic to PC12 pheochromocytoma cells, rat neuronal cultures, human neuroblastoma cell line SK-N-MC, but not U251 human glioblastoma cells nor muscle cells derived from the multipotent embryonic carcinoma cell line P19 [143].

Toxicity of CTFβ seen in in vitro studies has been supported in some in vivo studies, at least with over-expression systems. Several groups transplanted PC12 cells that were previously transfected with retroviral recombinants to over-express APP-CT104, or P19 cells engineered to over-express the same construct, into mouse brains [32, 93]. These studies reported evidence of cortical atrophy, loss of hippocampal granule cells and astrogliosis, concomitant to Aβ and APP immunoreactivity at 1–4 months after transplantation. Stereotactic injection of purified CT105 into brain resulted in dosage-dependent impairment in working memory, along with neurodegeneration and gliosis in the neocortex and hippocampus [125].

Many lines of transgenic mice have been created to examine C99 toxicity in vivo. One of the better-known transgenic lines created by Neve et al. [15, 59, 91, 92] expressed CT100 (with addition of a methionine residue to the N-terminus of C99) using brain dystrophin promoter. These mice exhibited Aβ deposits in cerebrovasculature and possibly in the parenchyma, dystrophic neurites in CA3 neurons and neuronal degeneration in the hippocampus [59, 93]. Subsequently, other lines of transgenic mice expressing a similar CT100 construct were shown to demonstrate reduced LTP and behavioral deficits [15, 91]. From these multiple lines of transgenic mice, it would appear that the CTF generated after β-secretase cleavage is neurotoxic and induced changes suggestive of AD pathology. However, not all CT100 transgenic animals exhibit age-dependent neuronal and synaptic degeneration: absent to milder phenotypes were seen in other transgenic mouse lines [111, 116]. Plasma Aβ levels do not correlate with brain deposits [31] although deposits can be found in muscle with associated myopathy when the cDNA is driven by a chimeric cytomegalovirus enhancer and chick β-actin promoter instead of the brain-specific promoters [55, 127], suggesting that differential promoter usage may contribute to the varied phenotypes observed. Not surprisingly, adding a familial AD (FAD) mutation (V717F) in the CT100 construct gave rise to phenotypes more severe than mice expressing wild-type CT100 [18, 72]. These mice

have reduced expression of NMDA receptor subunits, disrupted axonal morphology, increased number of TUNEL-positive cells in CA1, as well as increased hyperactivity at a young age and cognitive deficits [18].

Besides their in vitro and in vivo neurotoxicity, CTFs have also been implicated in the perturbation of ion channel activities, such as inducing strong nonselective inward currents in Xenopus oocytes [30], disturbing calcium and potassium channel activities and homeostasis [61], as well as free radical generation and inflammation [105]. Like the studies described above, these are all based on over-expression and whether these properties are present physiologically remains a difficult question to resolve.

Taken together, the weight of the evidence appears to support the notion that CTFs derived from β-secretase cleavage when over-expressed are toxic, and more so than CTFα. However, the studies described above have yet to pinpoint whether the toxicity is due to CTF itself or fragments derived from CTFβ, such as Aβ or AICD. It remains a curious mystery as to how the extra 16 amino acids from the N-terminus of Aβ can result in neurotoxicity, yet can be neurotrophic when appended to the C-terminus of APPs, as present in the sAPPα fragment.

Other N-terminal fragments

Besides cleavage of α-, β-, and γ-secretases, several studies have identified additional fragments of sAPP (generated by mechanisms other than α-, β-, or γ-secretase cleavages), which can be detected in human and rodent tissues [28, 102, 136]. In 2009, a lot of excitement was generated by findings from the Tessier-Lavigne lab centering on a sAPP fragment of about 35-kDa that appeared to act as a ligand for death receptor 6 (DR6, also known as TNFRSF21) to control axonal pruning [95]. The authors reported that degeneration induced by trophic deprivation was accompanied by enhanced β-secretase cleavage of APP to generate more sAPPβ and this toxicity was blocked by β-secretase but not by α-secretase inhibitors. Presumably, sAPPβ underwent further cleavage(s), possibly at APP286 after the E2 domain, to yield 2 bands of 55 and 35-kDa, the latter coined “N-APP”. This N-APP was shown to interact with DR6 to recruit caspase 3 (in cell bodies) and caspase 6 (in axons) to trigger degeneration [95]. Further, death in nerve growth factor-deprived sensory neurons cultured in compartment chambers was blocked in cells of Bax-deficient mice or after treatment with a BAX inhibitor, indicating that DR6 induced apoptosis through an intrinsic apoptotic pathway [95]. More recently, DR6 has been shown to contribute to the process of axonal pruning triggered by sensory deprivation via whisker trimming in adult mice, an example of experience-dependent axonal plasticity [77], and to complex with the p75 neurotrophin receptor [p75(NTR)], a known mediator of Aβ-induced neurotoxicity, to trigger neuronal cell death [50]. However, recent studies have revised the conclusions to exclude the requirement of β-secretase activity in DR6’s functions, and to highlight the C-terminal portion of the APP ectodomain containing the E2 sequence in DR6’s interaction with APP [57, 97].

In addition to the 35-kDa N-APP peptide, numerous other sAPP fragments have been described by mass spectrometry, including six APP fragments of approximately 12-kDa: $APP_{1–119}$, $APP_{1–121}$, $APP_{1–122}$, $APP_{1–123}$, $APP_{1–124}$, and $APP_{1–126}$ [102]. Studies using

HSV-1-mediated APP expression in the SH-SY5Y neuroblastoma cell line and rat cortical neuronal cultures also discovered an array of APP fragments, some of which were developmentally regulated and modulated by protein kinase C in a secretase-independent manner [28, 136]. It is not known what physiological roles these fragments play or whether they were generated after additional proteolysis of sAPP after secretion. However, within $APP_{28–123}$ lies a heparin-binding domain [109] that has been shown to interact with glycosaminoglycans and regulate APP dimerization. This cysteine-rich structure was also found to promote neurite outgrowth, which adds to the complexity of this discussion.

AICDs

Regardless of sequential cleavages by either α-secretase/γ-secretase or β-secretase/γ-secretase, a common end-product from these APP proteolytic events is a 5-kDa AICD that has been hypothesized to contribute to AD pathophysiology (Fig. 1a). The term AICD was named by analogy to the Notch intracellular domain (NICD), which is also cleaved from the Notch 1 cell surface receptor by γ-secretase and mediates the important signaling functions of this receptor [7]. Consequently, AICD has also been hypothesized to mediate transcriptional regulatory functions similar to NICD, but to date, demonstrating this activity conclusively has been difficult. The dominant AICD fragment is 50 amino acids in length, but other species, i.e., AICD48, AICD51 and AICD53, have also been identified and the cleavage event leading to the release of this fragment from APP has been designated as ε-cleavage [117]. Through a series of elegant studies, Ihara et al. have proposed that the γ-secretase complex first cleaves APP-CTFα and -CTFβ at the ε site to release AICD into the cytosol. Subsequent cleavages every 3 amino acids along the α-helical face of APP in the transmembrane region release Aβ peptides of 49–46–43–40 amino acids in length if the initial ε-cleavage released AICD 50, or Aβ peptides of 48–45–42–38 amino acids if starting from AICD 51 [142].

APP intracellular domains are short unstable peptides, hence, difficult to isolate and characterize [27, 62]. The intracellular portion of APP, which encompasses various AICD fragments, has been known to interact with many adaptor proteins to regulate intracellular cell signaling events (reviewed in [88]). Notably, the specific sequence Y_{682}ENPTY_{687} of AICD, a clathrin-mediated endocytosis motif, has been reported to interact with the Fe65 protein family (Fe65, Feb5L1), with Fe65 acting to stabilize AICD before translocation to the nucleus [62, 81].

When over-expressed in vitro and in vivo, AICD has been shown to induce apoptosis. For example, AICD is able to augment Fas-associated protein with death domain (FADD)-induced programmed cell death in AICD-transfected Jurkat cells [100]. Similarly, over-expressing AICD58 in human H4 neuroglioma cells resulted in apoptosis, which could be blocked by the pan-caspase inhibitor Z-VAD-FMK [63]. Mechanistically, AICD57 and AICD59 may induce toxicity on differentiated PC12 cells and rat primary cortical neurons by inducing the expression of glycogen synthase kinase 3β (GSK-3β) [60] or via a p53-mediated pathway [98]. However, a caveat of these studies is that they all expressed longer AICD fragments (>AICD51), which are not generated endogenously under basal conditions; hence, it raises the question as to the physiological relevance of these findings.

As mentioned above, by analogy to the Notch intracellular domain that is translocated into the nucleus to mediate Notch cell signaling events, it has been proposed that AICD regulates gene expression, via binding to Fe65 and undergoing translocation into the nucleus, where it may further complex with Tip60 and CP2/LSF/LBP [9, 22, 63] (Fig. 3). One of the genes proposed to be activated by this pathway is a tau-phosphorylating kinase, GSK-3β [60]. To test the potential in vivo activities of AICD, a bigenic transgenic mouse model that over-expressed both AICD59 and Fe65 (to stabilize AICD) in forebrain and hippocampal regions was developed [112]. Interestingly, these mice showed elevated activation of GSK-3β [112], an observation that correlates with age-dependent hyperphosphorylation and aggregation of tau protein as well as hippocampal neurodegeneration and working memory deficits [39], aberrant electrical activity and silent seizures [38, 137], and abnormal mossy fiber sprouting [38]. These effects can be blocked by the administration of the GSK-3β inhibitor lithium chloride [39]. However, other transgenic mouse lines over-expressing AICD50, AICD57, and AICD 59 failed to replicate these phenotypes or confirm the transcriptional role of AICD, even after crossing with human-tau-expressing transgenic mice [40, 41]. Whether this observed difference was due to the difference in the species and levels of AICD expressed, or the lack of Fe65 over-expression in these latter mouse lines, remains unclear.

Caspase-cleaved AICD derivatives: Jcasp and C31

Cleavage of APP, CTFs and AICDs after the Asp residue at position 664 by caspases or caspase-like proteases generates a 31 amino acid fragment at the C-terminal, termed C31. Cleavage of AICDs in particular also generates an additional small peptide at the N-terminal, termed Jcasp (Figs. 1b, 2).

Jcasp is a 2.8-kDa peptide that has been reported to have pro-apoptotic activities, but these initial findings have not been consistently reproduced [17, 76, 99, 100]. Several groups reported the tyrosine-dependent effects of transducing Jcasp into primary neuronal cultures that resulted in apoptosis, specifically Tyr653 of APP [17] by a pathway that appears to involve the SET protein (TAF1β, I2PP2A) [76]. However, it is worth noting that the Jcasp fragment used in these studies may not be present physiologically, because this fragment begins at Lys649 right after the transmembrane domain and is therefore N-terminally truncated, while the dominant AICD species is generated by ε cleavage between Leu645 and Val646 [117]. Further, Jcasp has not been isolated in any biological system, possibly due to its unstable nature. Appending GFP to its C-terminus to increase its stability did not result in significant cytotoxicity [99]. Similarly, while AICD was reported to be pro-apoptotic in Jurkat cells, Jcasp was not in another study [100]. Therefore, the nature of Jcasp and its putative toxicity remains unclear.

Cleavage of APP at position D664 was first described by multiple laboratories almost simultaneously in 1999, but the consequences of this cleavage event were not evident at the outset [19]. Although the P4–P1’ residues on human APP are VEVD/A, which is the cleavage motif for group II caspases (caspase-3 and -7), the precise caspase(s) that cleaves APP in vivo remains to be defined. Some groups suggested that executioner caspases (caspase-3, -6, and -7) are the main contributors in this D664 proteolytic event, while others concluded that apical caspases (caspase-2, -8, -9) as well as caspase-12 are responsible

(Table 1). This variability might be due to the different experimental protocols employed, as well as the different cell culture systems used.

Even though the identity of the caspase that cleaves APP at D664 remains controversial, the toxicity of the product formed from that cleavage (C31) is more evident, at least in vitro. For example, N2a neuroblastoma cells transfected with C31 or APP induced cell death [73] but the cytotoxicity was abrogated with an APP mutant construct where the Asp residue at position 664 was substituted by Ala (D664A) to inhibit cleavage (Fig. 2). In vivo confirmation of this cleavage event was detected in brains of AD individuals where the biochemical signature of APP cleavage and co-immunoprecipitates of APP and caspase-9 were reported [73].

Interestingly, C31 toxicity appears to be APP dependent [75]. Specifically, toxicity was minimal in B103 neuroblastoma cells that do not express either APP or APLPs [74, 75] but was enhanced when APP is co-expressed with C31 [75]. One model proposes that dimerization of APP results in recruitment of caspases that initiates cell death and this dimerization can be increased by soluble Aβ [74] (Fig. 2). Similarly, antibody-mediated cross-linking of APP can result in cell death [71]. Although this dimerization event could increase neurons' susceptibility to apoptosis, it requires an intact APP cytoplasmic domain because introducing the D664A mutation can attenuate cytotoxicity even in the presence of artificial cross-linking APP dimerization [74]. Similar results were seen in electrophysiological recording from cultured organotypic hippocampal slice culture where over-expression of CT100 carrying the D664A mutation could blunt Aβ-mediated synaptic depression and prevent loss of AMPAR- or NMDAR-mediated currents [84]. However, most of these studies relied on the over-expression of C31, which might not accurately reflect the physiological role in vivo.

To test the hypothesis of C31 toxicity in vivo, Galvan et al. generated APP transgenic mice over-expressing full-length APP encoding the Swedish and Indiana mutations (to drive amyloid pathology) and the D664A mutation [35]. Despite showing abundant amyloid deposits in brain, these mice exhibited rather normal morphological (presynaptic density and dentate gyral volumes) and electrophysiological (fEPSPs and LTP) characteristics, as well as behavior (spatial and working memory) as compared to control APP transgenic mice lacking this caspase cleavage site mutation [35, 36, 113]. It is important to note that this transgenic model did not "reverse" any existing pathology in the animals. Rather, the mouse lines showed the absence of anticipated or expected pathology. A subsequent re-examination of a high expressing D664A transgenic mouse line failed to reproduce the initial findings [47]; however, it was argued that this study lacked proper controls, rendering its results inconclusive [20]. Even though most transgenic mice with amyloid deposits demonstrate a number of phenotypes, such as synapse loss, defect in synaptic plasticity and behavioral impairments, not all APP transgenic mice show a similar array of deficits. Furthermore, the apparent lack of abnormalities in the PDAPP (D664A) transgenic mice could not be used to identify the mechanisms underlying the effects of the D664A mutation, i.e., whether the lack of neuronal dysfunction is due to loss of cleavage or absence of C31 generation, or due to changes in signaling events that were abrogated by this amino acid substitution. Thus, one cannot be certain that the lack of these predicted amyloid-associated alterations was due

specifically to the loss of the caspase cleavage site. Further experiments, such as targeted mutation of the caspase cleavage site in vivo in the absence of over-expression, will be needed to resolve the physiological importance of this cleavage event [94]. A summary of major neurotrophic and neurotoxic properties of APP and APP-derived fragments can be found in Table 2.

The –YENPTY– domain: beyond endocytosis

The preceding discussions have highlighted the difficulty in ascertaining the physiological roles of APP given the likelihood that the omnipresent APP proteolytic fragments may in fact be mediating the primary functions of APP, and possibly in opposing manners. With this caveat in mind, recent results from genetic targeting of APP in mice have yielded interesting findings, specifically concerning the –YENPTY– motif in the cytoplasmic domain of APP that is present in several of the previously mentioned fragments (Fig. 3).

Several studies have shown that APP, APLP1 and APLP2 single KO animals (where the entire YENPTY domain is absent) showed relatively mild phenotypes with diminished brain and body weight, reduced locomotor functions and grip strength, depressed LTP at older ages, minimal loss of synapses, and behavioral deficits [43]. However, APP knockin (KI) animals missing only the last 15 amino acid residues and lacking the YENPTY domain or the entire CTF after α-secretase cleavage were able to rescue a variety of deficits seen in APP KO mice, such as brain weight loss, grip strength and LTP deficits [107]. This would not be predicted if the YENPTY domain is critical to the physiological functions of APP. Indeed, observations from the KI mice suggested that the primary function of APP resides in the sAPPα extracellular fragment, as described earlier and that much of the CTF, including the YENPTY domain, is dispensable. In this context, it is quite surprising that a mouse with a targeted APP Y682G knockin mutation, where the first tyrosine residue of the YENPTY motif was substituted by glycine, exhibited developmental defects in the absence of Aβ deposition and accumulation [11, 80]. This would not be predicted given the mild phenotypes seen in mice where the C-terminus of APP was deleted. Even more interesting are the results when this Y682G mutation was introduced into an APLP2$^{-/-}$ background: the mice not only exhibited neuromuscular deficits but also early postnatal lethality very similar to that seen in APP/APLP2 double KO mice [10]. This is in contrast to the lack of developmental phenotype in APP T668A/APLP2$^{-/-}$ double mutant mice where alanine was substituted for threonine to inhibit phosphorylation at this residue thought to be important in Fe65 binding among other functions [11].

Indeed, it could be argued that the results from the Y682G mice might have been predicted from earlier in vitro studies showing the importance of the YENPTY sequence in modulating APP-dependent cell death activities [11, 60]. For example, this residue has been shown to play multifunctional roles as its phosphorylation state can modulate the binding and unbinding of various classes of adaptor proteins (Fig. 3). Specifically, when phosphorylated, Tyr682 creates docking sites for cytosolic protein such as Shc, Grb2, and Grb7, while inhibiting the binding of others, such as the Fe65 family of proteins; conversely, when dephosphorylated, binding of proteins containing a phosphotyrosine-binding (PTB) domain is impaired [79]. Interestingly, binding of Fe65 is also affected by phosphorylation

of Thr668, upstream of Tyr682, a binding site for the peptidyl-prolyl cis/trans isomerase, Pin1 [79]. This implies that post-translational modifications near the YENPTY domain can influence the interaction between APP and various adaptor proteins binding to this domain. It has been proposed that the phosphorylation of Tyr682 acts as a “biochemical switch” to facilitate APP’s interaction with numerous adaptor proteins [79]. In this way, Tyr682 and its phosphorylation status play intricate roles in modulating multiple downstream signaling events.

In sum, the Y682G mutant mouse has provided perhaps the strongest evidence that the YENPTY motif, specifically Tyr682, plays multiple and even contrasting roles in APP function. Through tyrosine phosphorylation and dephosphorylation, the interactions with various adaptor proteins are modulated in ways that result in distinctly different and perhaps even opposing cellular consequences. Therefore, when the entire YENPTY domain is deleted from knockout mice or mice with C-terminal APP truncations, all the interactions with the various cytosolic proteins are lost and the net outcome from abrogation of competing activities may be a rather bland phenotype. Whereas driving APP down only one of the pathways as seen in the Y682G KI mouse illuminates one aspect of APP function that was not seen in the knockout mice. Whether this motif comes into play as a part of full-length APP or as part of the APP C-terminal fragment is unclear and is another interesting question to ponder. But the answer to this question will likely require the generation of additional APP gene-targeted mouse lines for detailed analyses.

Conclusion

Even though the basic mechanisms underlying synaptic injuries in AD remain to be elucidated, much insight has been gained from the past decade that complements the early studies completed soon after the identification of the APP gene. Rather than focusing on the Aβ peptide, which some might argue has been overly emphasized, this review has focused on the non-Aβ peptides derived from APP to highlight the physiological and possibly pathophysiological roles of the amyloid-independent pathways. Thus, the intent is to provide a fuller picture of the putative physiological roles of various APP fragments in generating both APP-dependent and perhaps Aβ-independent trophic and toxic properties. Indeed, early studies on APP function may have unfortunately disregarded the roles played by the proteolytic fragments. However, we hope this review emphasized the difficult task to generate unambiguous results on individual APP fragments given the obligatory presence of these fragments, especially in the context of over-expression. Nonetheless, a comprehensive understanding of AD pathophysiology will likely have to come from not only the roles played by Aβ peptides, but also from the roles played by the other APP proteolytic products. Almost three decades after the identification of the APP gene and its gene products, the question of how this molecule contributes to AD pathophysiology continues to fascinate us.

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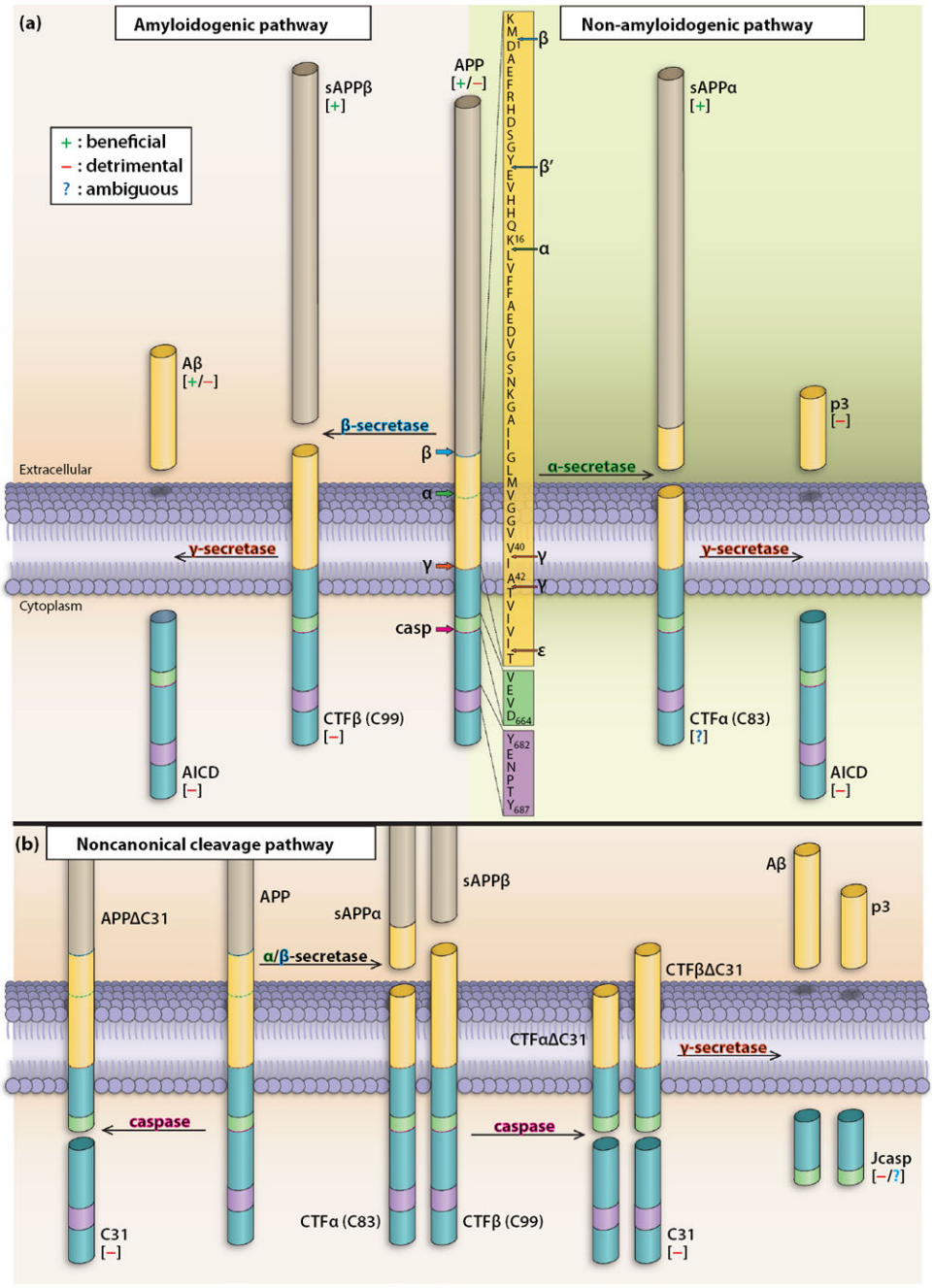

Fig. 1.

APP processing and cleavage products. **a** The *right-hand panel* illustrates the non-amyloidogenic APP processing pathway, which is initiated by α-secretase cleavage, whereas the *left-hand panel* depicts the amyloidogenic processing pathway as initiated by β-secretase cleavage. Both secretase-mediated cleavage events generate soluble ectodomains of APP (sAPPα and sAPPβ) and two membrane-tethered C-terminal fragments (CTFα and CTFβ, also known as C83 and C99). Subsequent cleavage within the transmembrane domain by γ-secretase yields the 3-kDa peptide p3 and the 4-kDa Aβ, respectively, along with the release

of the cytoplasmic polypeptide termed AICD. The amino acid sequences (with numbering based on the APP695 isoform) are shown for three domains of significance: (1) the $A\beta_{1–42}$ sequence that begins with D^1 and ends with A^{42}; (2) the $VEVD_{664}$ sequence, which is a putative caspase cleavage motif; and (3) the $Y_{682}ENPTY_{687}$ sequence, which is a clathrin-mediated endocytosis motif that has been shown to modulate several APP functions through phosphorylation and dephosphorylation of the first tyrosine residue. The physiological functions of APP and its cleavage products have been classified as primarily beneficial, detrimental, or ambiguous depending on our judgment of where the weight of the evidence lies; this is meant only as a rough introduction to these multifunctional peptides. For example, we have categorized sAPPα as beneficial, as it is largely associated with trophic effects, although it should be noted that over-expression can lead to a tumorigenic phenotype. **b** APP processing can also proceed down a non-canonical pathway, where it is thought that caspase cleavage after $VEVD_{664}$ results in additional fragments, including Jcasp (from the N-terminus of AICD to D_{664}) and C31 (from the caspase cleavage site to the C-terminus of APP), along with various APP and CTFs lacking the last 31 amino acids

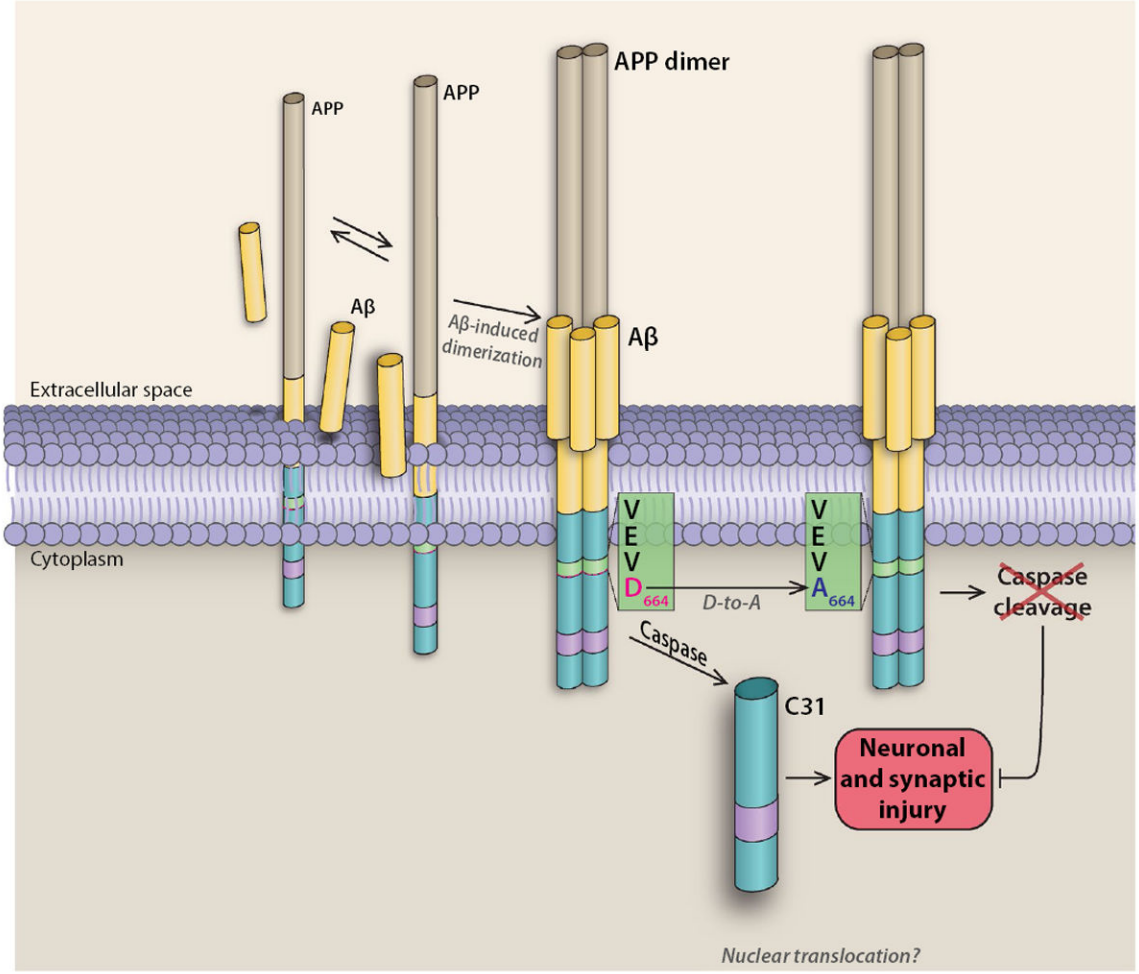

Fig. 2.

Caspase-mediated APP cleavage generates the neurotoxic C31 species. A proposed model of C31 generation is presented here, wherein Aβ binding promotes APP dimerization, resulting in caspase cleavage after D_{664} and generation of the C31 peptide. C31 has been shown to cause synaptic dysfunction and neuronal death, effects which are mitigated by alanine substitution at residue D_{664}, presumably due to abrogated caspase cleavage and consequent blockage of C31 production

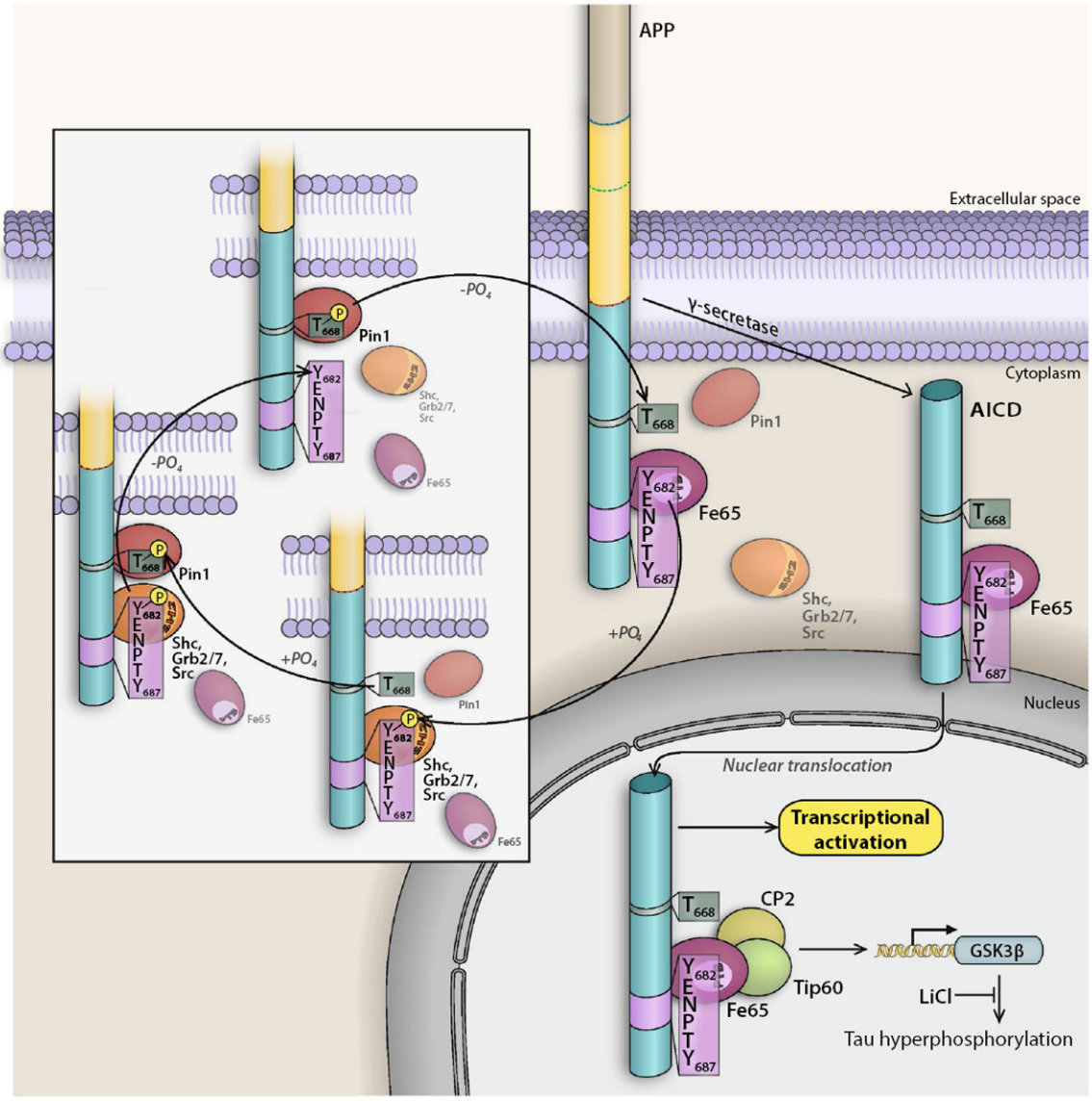

Fig. 3.

AICD and the YENPTY domain of APP. γ-secretase cleavage of APP generates AICD, typically a highly unstable molecule, although binding to Fe65 family members results in its stabilization and translocation to the nucleus. This complex, in association with CP2/LSF/LBP and Tip60, has been shown to transactivate *GSK-3β*, with kinase upregulation leading to tau hyperphosphorylation, which can be inhibited by lithium chloride treatment. Proteins containing phosphotyrosine-binding (PTB) domains, such as the Fe65 family members, bind to APP when Y_{682} is dephosphorylated, but their binding is inhibited when Y_{682} is phosphorylated (as shown in the *right-hand inset box*, going counterclockwise), which conversely promotes the binding of SH2 domain-containing proteins like Shc, Grb2/7, and Src. Phosphorylation of T_{668} in addition to Y_{682} promotes binding of the Pin1

isomerase and further potentiates binding by SH2 domain proteins, while phosphorylation of only the T_{668} residue inhibits this interaction

Table 1

Summary of caspases involved in the generation of C31

Caspases	References
Apical caspases	
2	[134]
8	[73, 75, 82, 101, 140]
9	[73, 75]
Executioner caspases	
3	[13, 34, 37, 45, 52, 82, 135]
6	[34, 70, 82, 100, 101]
Other caspase	
12	[90]

Table 2

Summary of major neurotrophic and neurotoxic properties of APP and APP-derived fragments

	Normal functions/neurotrophic properties	Neurotoxic properties	Primary site of action (proposed)
FL-APP	Cell adhesion	Neurodegeneration when over-expressed	Extracellular space
	Cell surface receptor (via cytoplasmic domain)	Neurodegenerative changes in APP triplication (trisomy 21 in humans and trisomy 16 in mice)	
	Promote cell division		
	Promote synapse formation and maintenance		
	Promote synaptic plasticity		
	Iron transport		
	Neuroprotective (to Aβ and glutamate toxicity)		
Aβs	Transcription factor	Inhibition of LTP and synaptic transmission by low-n soluble Aβ oligomers	Extracellular and intracellular spaces
	Kinase activation		
	Cholesterol transport	Synaptic injury	
	Antimicrobial	Cognitive impairment	
	Neuroprotective against oxidative stress (Aβ40)		
	Promote neurogenesis and neurite outgrowth (Aβ40)		
p3	None reported	Cytotoxic in culture	Extracellular space
		Promote inflammatory responses	
sAPPα	Trophic properties in neurons and non-neural cells	Unregulated cell growth (promote tumorigenesis)	Extracellular space
	Neuroprotective	Stimulate microglia activation	
	Promote stem cell proliferation	Produce proinflammatory products	
	Enhance memory functions		
sAPPβ	Similar to sAPPα (100 fold less potent)	Similar to sAPPα	Extracellular space
CTFα	Steer the system away from the amyloidogenic pathway	None reported	Intracellular space
CTFβs	None reported	Cytotoxicity to neurons and non-neural cells	Intracellular space
		Neurotoxic following direct intracranial injection	
		Perturb ion channel activities and homeostasis	
		Promote astrogliosis	
		LTP impairment	
		Cognitive impairment	
AICDs	Mediate transcriptional activity	Pro-apoptotic	Intracellular space, nucleus
	Activity may be dependent on translational modification at YENPTY motif and interaction with cytosolic adaptor molecules	Activate GSK-3β to induce toxicity	
		Degeneration in hippocampal neurons	
		Induce aberrant electrical activity and silent seizures	
		Cognitive impairment	
Jcasp	None reported	Pro-apoptotic	Intracellular space
C31	None reported	Pro-apoptotic, neurotoxic	Intracellular space
		Generated following caspase cleavage	
		Toxicity is APP dependent	