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Review

# A TAG on to the neurogenic functions of APP

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**The proteolytic processing of amyloid β precursor protein (APP) has long been studied because of its association with the pathology of Alzheimer's disease (AD). The ectodomain of APP is shed by α- or β-secretase cleavage. The remaining membrane bound stub can then undergo regulated intramembrane proteolysis (RIP) by γ-secretase. This cleavage can release amyloid β (Aβ) from the stub left by β-secretase cleavage but also releases the APP intracellular domain (AICD) after α- or β-secretase cleavage. The physiological functions of this proteolytic processing are not well understood. We compare the proteolytic processing of APP to the ligand-dependent RIP of Notch. In this review, we discuss recent evidence suggesting that TAG1 is a functional ligand for APP. The interaction between TAG1 and APP triggers γ-secretase-dependent release of AICD. TAG1, APP and Fe65 colocalise in the neurogenic ventricular zone and in fetal neural progenitor cells in vitro. Experiments in TAG1, APP and Fe65 null mice as well as TAG1 and APP double-null mice demonstrate that TAG1 induces a γ-secretase- and Fe65-dependent suppression of neurogenesis.**

## Shedding and RIPping of APP

Amyloid β precursor protein (APP) has been the subject of intensive study because of its association with the pathology of Alzheimer's disease (AD). APP is a type I transmembrane glycoprotein cleaved by specific proteases, sheddases, to shed a large, secreted, soluble luminal or extracellular domain (APPs) leaving a membrane-bound stub[1] (see Fig. 1). The remaining membrane-bound stub then undergoes regulated intramembrane proteolysis (RIP)[2] by an intramembrane cleaving protease (I-CLIP), the γ-secretase complex.[3]

Initial ectodomain shedding is a common feature of the proteolytic processing of many type I and type II transmembrane proteins. In the case of APP, the sheddases responsible for ectodomain secretion are α- or β-secretases. Cleavage by α-secretase, which is mediated by members of the ADAM (a disintegrin and metalloproteinase) family of proteinases, including in particular ADAM 10 and ADAM 17,[4-8] results in secretion of APPsα and retention of a membrane-tethered C83 stub, also known as C-terminal fragment α (CTFα). Cleavage by β-amyloid-cleaving enzyme-1 (BACE) or β-secretase, results in secretion of APPsβ and retention of a membrane-tethered C99 stub, also known as C-terminal fragment α (CTFβ).[9]

After ectodomain shedding of the APPs, the remaining C-terminal fragment still tethered to the membrane can undergo RIP by the γ-secretase complex.[2,10] Cleavage by the γ-secretase complex releases the C-terminal APP intracellular domain (AICD, also sometimes known as AID or C-terminal fragment γ, CTFγ) and simultaneously a small N-terminal fragment. Following cleavage by α-secretase the N-terminal fragment is the nonamyloidogenic, p3. However, following cleavage by β-secretase the N-terminal fragment is the potentially amyloidogenic, Aβ. The γ-secretase complex minimally contains a quartet of proteins:[11,12] presenilin 1 or 2 (PS1 or PS2), nicastrin, anterior pharynx-defective phenotype-1 (Aph-1) and presenilin enhancer (Pen-2).[13-16] Nicastrin appears to act as a receptor ensuring that the luminal or extracellular N-terminal of the sheddase cleaved substrate is of the correct length,[17] which means that ectodomain shedding is required for γ-secretase-dependent RIP to proceed.[3,12] Aph-1 appears to act as a scaffold to which first nicastrin and then presenilin and Pen-2 are bound. Pen-2 then triggers endoproteolysis of presenilin into an active heterodimer.[3,12] The γ-secretase complex is thought to cleave the membrane bound C-terminal fragment of APP at multiple sites: referred to as γ, ζ and ε. The γ site is variable and can occur at amino acids 38, 40 and 42 in the C99 stub left by BACE-mediated ectodomain shedding via cleavage at the β-secretase site.[18] The generation of Aβ40 and Aβ42 are most common and an increase in the ratio of Aβ42 to Aβ40 can increase the risk of polymerization and amyloid deposition.[18] Cutting at the ε-site at amino acid 49, also known as the S3-like site by analogy with Notch, leads to release of AICD.[3,19] It appears the γ-secretase complex may cut first at the ε-site and then cut back every helical turn of the Aβ substrate to generate the γ-site cleavage products.[20,21] Although in theory the cleavage of the APP substrate should always generate equimolar amounts of Aβ and AICD,[20] it appears that Aβ and AICD generation are not directly linked and can be independently modulated by mutations of APP[22] or knockdown of TMP21 another protein that may serve as an additional modulatory subunit in the γ-secretase complex.[23]

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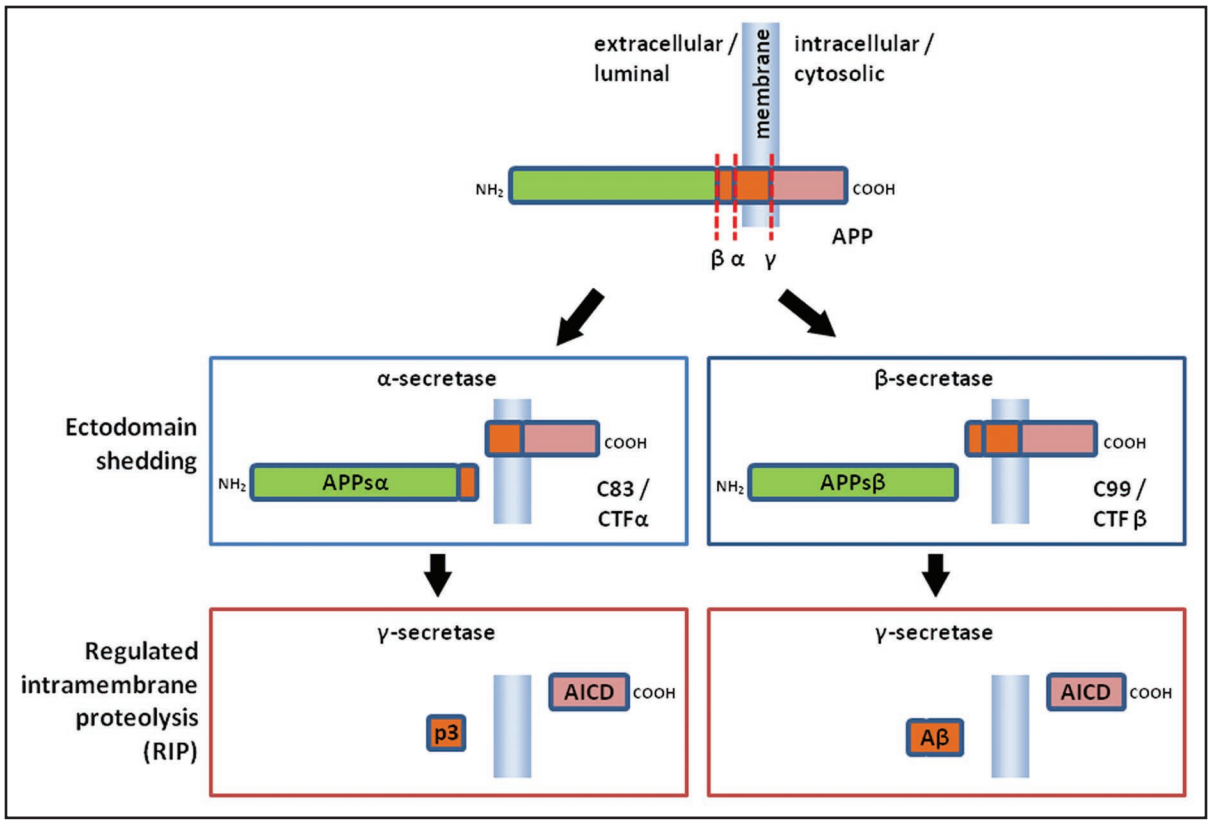


Figure 1. A schematic diagram of amyloid β precursor protein (APP) proteolytic processing (not drawn to scale). APP is a large transmembrane molecule (unboxed at top). There is a large extracellular or luminal domain with β- and α-secretase cleavage sites (β and α, respectively) close to the membrane. The γ-secretase sites (γ) occur within the transmembrane region. On proteolytic processing the ectodomain is first shed by either α- or β-secretase mediated cleavage (middle, left and right boxes, respectively). Cleavage by α-secretase (box at middle left) releases APPsα extracellularily or luminally and leaves a C83 (also known as CTFα) stub in the membrane. Cleavage by β-secretase (box at middle right) releases APPsβ extracellularly or luminally and leaves a C99 (also known as CTFβ) stub in the membrane. Regulated intramembrane proteolysis (RIP) by γ-secretase subsequently cleaves the stubs remaining in the membrane (bottom). Cleavage of C83 (box on bottom left) liberates p3 and the APP intracellular domain (AICD). Cleavage of C99 (box on the bottom right) liberates amyloid β peptide (Aβ) and the APP intracellular domain (AICD).

## Physiological Functions of Proteolytic Processing of APP

As the secretase-mediated proteolytic processing of APP can lead to potentially harmful production of Aβ, it is a puzzle as to why it exists. It may in part be that selection pressure against production of Aβ42 has not been great since its deleterious effects are usually not seen until late in life and so may have little impact on reproductive success. However, it has been speculated that proteolytic processing of APP may serve important physiological functions in inter- and intracellular signaling, which unfortunately have the potential to produce Aβ42 as a byproduct. Although most of the literature on APP has focused on its potential pathological roles in the development of AD, in recent years there has been increasing interest in the physiological functions of APP.

APPs has been implicated in diverse cellular processes involved in cell proliferation, cell survival, neuroprotection, enhancement of memory, neuronal excitability and regulation of synaptic plasticity.[24-29] Expression of APPsα was sufficient to recover anatomical, behavioral and electrophysiological abnormalities of APP-deficient mice[30] suggesting that many of the physiological functions of APP are served by the secretion of APPsα. APPs also controls neural stem cell division in the adult subventricular zone.[31] The N-terminal region of APPs was reported to stimulate neural stem cell proliferation[32,33] and APPsα was found to bind to EGF expressing neural stem cells in the subventricular zone and in combination with epidermal growth factor (EGF), to stimulate proliferation of neural stem cells in vitro.[34]

One view of the role of the γ-secretase cleavage has been that it serves to facilitate protein turnover after secretion of the APPs.[3,12] The release of the AICD allows removal of the protein stubs from the membrane and subsequent intracellular proteosomal degradation. Indeed, the γ-secretase complex has even been dubbed the "proteosome of the membrane."[35,36] An alternative view is that the γ-secretase proteolytic products of the N-terminal stubs left in the membrane may also serve physiological functions in inter- and intracellular signaling. In addition to its pathological role in amyloid deposition in AD, the Aβ generated by γ-secretase RIP following β-secretase cleavage appears to play more direct roles in regulation of cell death. It had been reported that binding of the antibody 22C11 to the extracellular domain of APP activated G protein $G_o$-dependent signaling[37] and that the familial AD (FAD) mutations of APP that constitutively activated $G_o$ triggered apoptosis via the Gβγ subunit complex.[38] It has now been reported that Aβ, which binds to APP causing clustering of APP in the membrane,[39] acts as an APP ligand triggering $G_o$ protein activation-mediated neuronal degeneration.[40]

## Physiological Functions of AICD

The hypothesis that AICD may also serve signaling functions has been more controversial. Investigation of the functions of AICD was long overshadowed by the widely recognized pathological importance of Aβ. One of the reasons why AICD received little attention may be that it is unstable and short-lived and so was difficult to detect. However, the transient nature of AICD is itself consistent with the notion that AICD may serve an intracellular signaling function. γ-secretase complex-mediated RIP cleaves not only APP but also many other Type I transmembrane proteins, including Notch.[3,10,41-43] In the case of Notch, RIP clearly serves an important role in regulation of intracellular signaling by the Notch intracellular domain (NICD). Notch, like APP, is first cleaved by a metalloprotease sheddase, ADAM 17 or tumor necrosis factor (TNF) α-converting enzyme (TACE), just outside the membrane to shed the transmembrane stub.[10,44,45] Then, the transmembrane stub of Notch undergoes RIP mediated by presenilin-dependent γ-secretase[46] cleaving the protein at an intramembrane site (S3) to release the NICD, which translocates to the nucleus.[47] In the nucleus, NICD acts as a second messenger to modulate target gene expression.[48,49] Depending upon the factors and cofactors recruited, NICD can act by at least two distinct pathways in the nucleus. In one pathway, NICD can bind to a complex containing CSL (CBF1/RBP-J in vertebrates, suppressor of hairless in Drosophila and Lag-1 in C. elegans) DNA-binding proteins and other proteins, including the coactivator Mastermind (Mam) and Ski-interacting protein (SKIP),[50-54] converting this CLS protein complex from a repressor of transcription to an activator of transcription.[55] As yet, surprisingly few immediate target genes have been identified for this ubiquitous Notch signalling pathway.[56] Two targets are the hairy/enhancer of split (HES) and HES-related (HERP) repressor protein families of transcription regulators.[57-60] HES represses the expression of a group of proneural differentiation, basic helix-loop-helix (bHLH) genes, including NeuroD, Mash, Math and Neurogenins.[61-63] In the other distinct pathway, cytosolic NICD recruits Deltex1 and translocates it to the nucleus where, by binding to transcriptional activator p300, the NICD-Deltex1 complex inhibits transcriptional activation by Mash1.[64,65] NICD-dependent transcriptional activity is now known to play an important role in many cellular functions including cell proliferation, differentiation and apoptosis.[54,60,66]

By analogy to NICD, it might be hypothesized that AICD could serve as an intracellular signaling molecule, perhaps even modulating transcription.[67] One mechanism by which AICD could achieve this may be by binding to Numb and thus inhibiting Notch-mediated signaling.[68] Alternatively, AICD might more directly acts as a regulator of transcription or a modulator of another regulator of transcription. The hypothesis that AICD can modulate transcriptional activity has been highly controversial. Several studies have suggested that AICD can regulate transcription of various endogenous genes, including *KAI1*, *GSK-3*β, *APP*, *BACE*, *neprilysin*, *α2-actin*, *transgelin* and *EGFR*.[69-74] Yet others did not find any evidence for AICD-mediated regulation of the transcription of *KAI1*, *GSK-3*β, *APP* and *neprilysin*.[75-77] It has also been highly controversial as to whether AICD is translocated to the nucleus[78,79] or modulates transcription while still bound to the membrane through interaction with scaffolding or transcriptional regulatory proteins.[80,81] Initially, it appeared that AICD is stabilized by Fe65, interacts with the transcriptional factor Tip60 and translocates to the nucleus.[78] In experiments using an artificial reporter system in which Gal4 was fused to the N-terminal of AICD such that it could be released by γ-secretase-dependent cleavage and expression of a luciferase reporter driven by the interaction of the Gal4 with the Gal4 response element, AICD appeared to have transcriptional activity in complex with Fe65 and histone acetyltransferase Tip60.[79] However, this study using an artificial reporter system does not demonstrate whether AICD itself is involved in endogenous transcriptional activation. Even the question of whether endogenous AICD translocates to the nucleus remains unresolved. Later studies indicated that membrane-tethered AICD recruits and activates Fe65 allowing its translocation to the nucleus but that it is not essential for Fe65-dependent transcriptional transactivation.[81] Moreover, a subsequent study confirmed that Fe65 alone was sufficient for transcriptional transactivation and that APP and Tip60 play positive and negative modulatory roles, respectively.[82] While, yet another study suggested that APP stabilizes Tip60 through CDK-dependent phosphorylation allowing APP to signal to the nucleus by a γ-secretase-independent mechanism.[83] Investigation of the phosphorylation of APP at Thr688 (residue numbering for the APP695 form), which reduces or prevents Fe65 binding to APP[84] and disrupts the stabilization of AICD by Fe65 binding,[85] suggested that activation of Fe65 may involve liberation from membrane bound APP on phosphorylation and that unphosphorylated, but not phosphorylated, AICD translocates to the nucleus independently of Fe65.[80] Thus the role of AICD in Fe65/Tip60-mediated transcriptional activity remains unclear. However, in the case of the epidermal growth factor receptor (EGFR), direct binding of endogenous AICD to the EGFR promoter is reported.[74] It has also been suggested that AICD can enhance the transcriptional activation of another transcription factor, p53.[86] The evidence falls short of conclusively demonstrating that AICD is in itself a transcription factor or a nuclearly translocated modulator of transcription factors. Nevertheless, together the literature suggests the possibility that intracellular release of ACID could serve as an intracellular signal, perhaps even playing a role in the modulation of the expression of certain proteins.

## TAG1-APP Ligand-Receptor Triggered Release of AICD

An important aspect of the cellular function of the RIP of Notch is that the γ-secretase mediated cleavage of NICD is stimulated by ligand binding to Notch. At the cell surface, the Notch receptor responds to ligand binding to its extracellular epidermal growth factor (EGF)-like repeats.[87] Delta, Serrate and Lag (DSL) family proteins can bind to Notch and stimulate ectodomain shedding.[45,61,88] Consistent with the notion that the γ-secretase complex senses whether the N-terminal stub has been sufficiently cleaved via nicastrin,[17] it appears that ligand-induced extracellular cleavage regulates γ-secretase-mediated proteolytic activation of Notch1.[89] Recently, we have shown that F3/contactin and its homologue NB-3 are functional ligands for the Notch receptor. Activation of Notch by these F3/contactin family proteins modulates oligodendrocyte differentiation via the transcriptional factor Deltex.[56,90-92]

By analogy with the RIP of Notch, one might predict that ligand interaction with APP might stimulate release of AICD. It was reported that f-spondin binds to the extracellular domain of APP and inhibits β-secretase cleavage.[93] Could a ligand bind to APP

promoting, rather than inhibiting, ectodomain shedding of APP and thus facilitating γ-secretase cleavage in a manner similar to ligand-activation of Notch RIP? We investigated the interaction between TAG1, a member of the F3/Contactin family of glycophosphatidylinositol (GPI)-linked proteins, and APP.[94] Cell adhesion, coimmunoprecipitation and pull-down assays all suggested that APP and TAG1 bind to each other. Using the artificial luciferase reporter system in which Gal4 is fused to the N-terminal end of AICD adjacent to the γ-secretase ε cleavage site,[79] we investigated whether the TAG1-APP interaction could trigger intracellular release of AICD and hence activate the Gal4 promoter driven luciferase reporter. We found that TAG1 stimulated activation of the luciferase reporter and that this activation was dose-dependently blocked by two different γ-secretase inhibitors indicating that TAG1 triggers AICD release in a γ-secretase-dependent manner. Moreover, Western blotting confirmed that TAG1 dose-dependently increased expression of AICD. Thus, it appears that TAG1 is a novel ligand for APP capable of facilitating γ-secretase-dependent release of AICD. This suggests that APP may function as a receptor for TAG1 in a manner similar to that in which Notch functions as a receptor for DSL and F3/NB3 (Fig. 2).

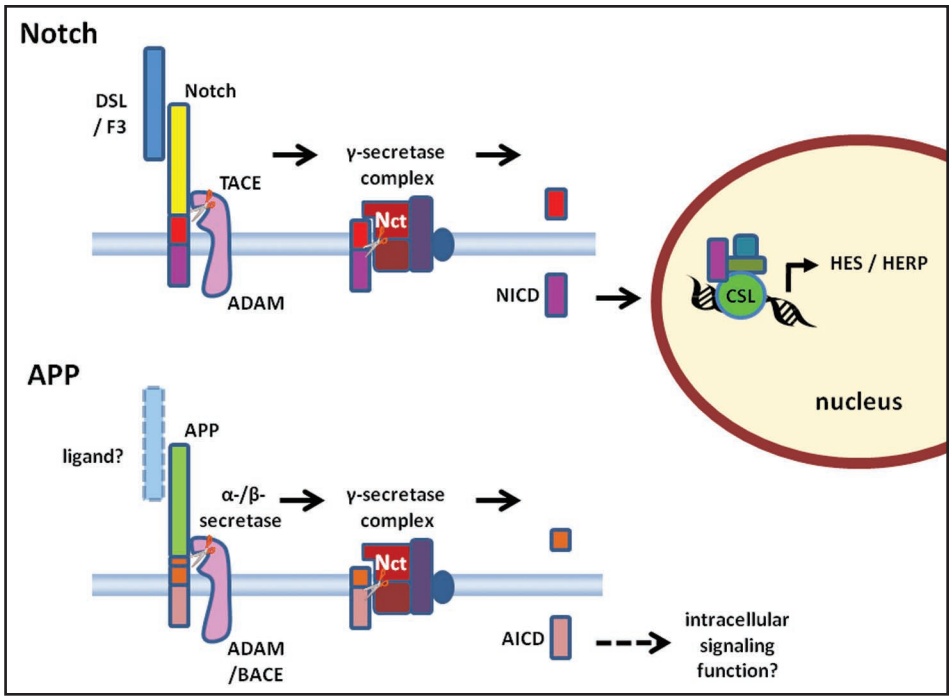


Figure 2. A schematic diagram of ligand-dependent γ-secretase cleavage of Notch (top) and associated intracellular signaling compared with proteolytic processing of APP (bottom) (not drawn to scale). A Delta, Serrate and Lag (DSL) or F3/contactin family protein (F3) acts as a ligand binding to the extracellular domain of Notch. Binding of the ligand stimulates ectodomain shedding by tumour necrosis factor (TNF) α-converting enzyme (TACE), a disintegrin and metalloproteinase (ADAM). Similarly, the extracellular portion of APP is cleaved by α-secretase, an ADAM, or β-secretase, β-amyloid-cleaving enzyme-1 (BACE). Nicastrin (Nct) in the γ-secretase complex acts as a receptor interacting with the extracellular N-terminal of the protein stub left in the membrane. Only when the ectodomain has been shed can γ-secretase cleavage of the membrane bound stub proceed. The γ-secretase-dependent cleavage releases the Notch intracellular domain (NICD) in the case of Notch and the APP intracellular domain (AICD) in the case of APP. NICD is known to serve as an intracellular signaling molecule regulating protein expression on translocation to the nucleus. In the example illustrated in the diagram, NICD complexes with CSL and other proteins to regulate expression of the hairy/enhancer of split (HES) and HES-related (HERP) repressor protein families of transcription regulators.

## Physiological Function of TAG1-APP Interaction in Neurogenesis

If TAG1 is a ligand for APP, what physiological functions does this ligand-receptor interaction mediate? In the central nervous system (CNS), GPI-linked recognition molecules, such as TAG1, NB-3 and F3/contactin, have been implicated in key developmental events, including selective axonal fasciculation, neural cell adhesion and migration, and neurite outgrowth.[95] TAG1 is expressed from early in development, for example on the cell bodies of motor neurons in spinal cord at E10.5 and during their lateral migration from the ventricular zone at E13.[95] Likewise, APP is expressed early in neural development. APP mRNA transcripts are reported in mouse oocytes and early in mouse embryogenesis.[96] In the mouse neural tube, APP is expressed as early as E9.5, when the neural stem cells and RC2-positive radial glia are actively dividing.[97] APP is expressed by neuroepithelial cells in the cortical ventricular zone, particularly in the apical portion where mitosis takes place at E14 to E16.[98] APPsα binds to EGF-positive fetal neural stem cells from the cortical subventricular zone and, together with EGF, APP stimulates proliferation of the cells from embryonic neurospheres in vitro.[34] A recent in utero RNA interference study indicated that Aβ plays a critical role in neural migration.[99] It has also been reported that neurogenesis is increased in an AD mouse model[100] and in the adult human hippocampus in AD,[101] although the changes in neurogenesis in AD and their implications are controversial.[102] Together these data suggest that TAG1 and APP may both be involved in neural development.

We found that TAG1 and APP colocalize in the neurogenic niche of the ventricular zone in the developing mouse brain and within neural progenitor cells (NPCs) isolated from this region.[94] NPCs isolated from TAG1 null and APP null mice showed abnormally enhanced neurogenesis, suggesting that TAG1 and APP are involved in negative regulation of neurogenesis. Moreover, consistent with the notion that TAG1 and APP act by a common pathway rather than by two separate and additive pathways, NPCs from TAG1/APP double null mice showed a similar enhancement in neurogenesis to NPCs from single TAG1 and APP null mice. Treatment with soluble TAG1 protein during differentiation normalized neurogenesis in NPCs isolated from TAG1 null mice but not in NPCs isolated from TAG1/APP double null mice. Moreover, transfection of NPCs isolated from TAG1 null mice with AICD rescued the suppression of neurogenesis. Thus, it appears that binding of TAG1 to APP can trigger an AICD-dependent suppression of neurogenesis. As Fe65 has been proposed as a partner of AICD in intracellular signaling mechanisms,[78,79,81,84] we also investigated the

localization of Fe65. Fe65 colocalized with TAG1 and APP in the fetal cortical ventricular zone and NPCs isolated from fetal brain.[94] NPC's isolated from Fe65 null mice also showed a similar enhancement of neurogenesis to that observed in NPCs isolated from TAG1, APP and TAG1/APP null mice. Using a Gal4 promoter-driven luciferase reporter system in which Gal4 was fused to the N-terminal of Fe65 we showed that cotransfection of TAG1-transfected cells with APP led to increased reporter activity indicative of mobilization of Fe65. But cotransfection of TAG1-transfected cells with an NPTY to NATA mutation that abolishes Fe65 binding[84] did not increase reporter activity. Transfection of NPCs derived from TAG1 null mice with AICD with the same NPTY to NATA mutation abolishing Fe65 binding did not rescue the suppression of neurogenesis. Thus these data suggest that Fe65 is required for the AICD-dependent suppression of neurogenesis by TAG1.

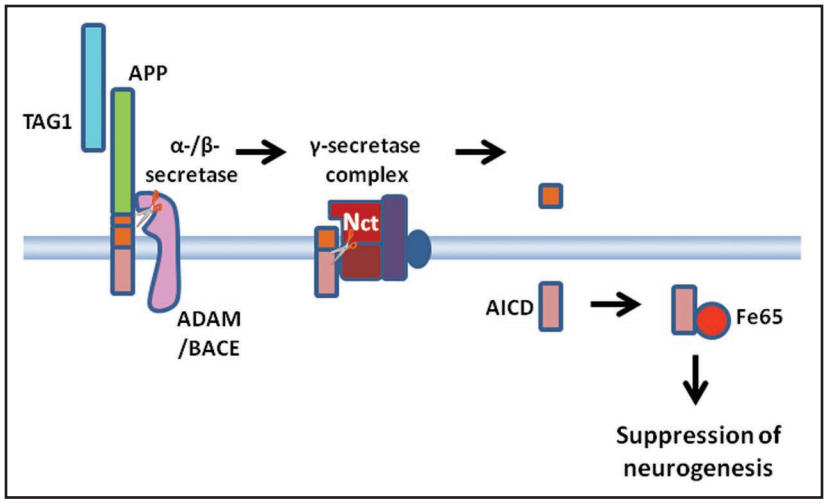


Figure 3. A diagrammatic summary of a working model of TAG1-APP signaling. TAG1 is a ligand for APP. When TAG1 binds to APP this stimulates or facilitates ectodomain shedding by α- or β-secretases. Once the ectodomain has been shed, γ-secretase cleavage of the membrane bound stub can proceed. Thus, TAG1 binding leads to γ-secretase-dependent cleavage releasing ACID intracellularly. AICD interacts with the scaffolding protein, Fe65. This results in an Fe65-dependent suppression of neurogenesis.

## Conclusions

Together, our data[94] are consistent with the hypothesis that TAG1 binding to APP stimulates γ-secretase-dependent cleavage of APP to release AICD which suppresses neurogenesis by a mechanism involving Fe65 (Fig. 3). At this stage the mechanisms by which AICD suppresses neurogenesis are unknown. It may be interesting to investigate whether AICD acting in concert with or through modulation of Fe65 influences gene transcription. The discovery that TAG1 can act as an AICD-releasing ligand for APP suggests the possibility that other molecules may likewise act as ligands of APP. It may be interesting to investigate whether ligand-stimulated cleavage of APP is involved in physiological regulation of other cellular functions. Our finding that TAG1 binding to APP triggers AICD cleavage may also have implications in AD. It may be of interest to investigate whether ligand-stimulated cleavage influences the probability of amyloidogenic cleavage of APP. Conversely, abnormal proteolytic processing of APP in AD may have consequences for intracellular signaling.

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