APP at a glance

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Journal of Cell Science 120, 3157-3161
Published by The Company of Biologists 2007
doi:10.1242/jcs.03481

The characteristic cerebral plaques of Alzheimer disease (AD) are primarily composed of an aggregation-prone 39-43-residue peptide called amyloid β (Aβ), which is a proteolytic product derived from the amyloid β precursor protein (APP), a type I integral membrane protein (Hardy and Selkoe, 2002). The discovery of the APP gene was followed by the identification of missense mutations associated with familial, early-onset AD (FAD). These mutations are found in and around the Aβ region of APP, and affect the production or aggregation properties of Aβ. Those APP mutations near the C-terminal region of the Aβ sequence specifically lead to increased proportions of the highly aggregation-prone 42-residue form of Aβ (Aβ42). Although two other APP-like proteins – APLP1 and APLP2 – are known, the Aβ regions are not well conserved, and no FAD mutations have been identified in these genes.

Production of Aβ involves sequential proteolysis by β- and γ-secretases, the former being a membrane-tethered protease and the latter a membrane-embedded complex with presenilin as the catalytic component (Haass, 2004). Presenilins are also sites of many FAD-associated missense mutations which alter the γ-secretase cleavage event to skew production towards Aβ42. Together, these findings strongly supported the hypothesis that this peptide is indeed a pathogenic entity for AD. Besides presenilin, which is an unusual intramembranous aspartyl protease (Xia and Wolfe, 2003), other members of the γ-secretase complex include the membrane proteins nicastrin, APH1, and PEN2; this protease complex cuts within the transmembrane domain of APP and determines the length of Aβ peptides. The pepsin-like aspartyl protease β-secretase sheds the ectodomain of APP, releasing the soluble protein sAPP-β. Alternative shedding by metalloproteases called α-secretases (e.g. ADAM17) leads to proteolysis within the Aβ region and produces a slightly longer soluble protein sAPP-α. After ectodomain shedding, γ-secretase cuts the remaining membrane-
bound stub to release the APP intracellular domain (AICD) as well as either Aβ (via the β-secretase pathway) or the N-terminally truncated peptide p3 (via the α-secretase pathway). Aβ in turn can be degraded by proteases such as the insulin-degrading enzyme (IDE) (Farris et al., 2001) and nephrilysin (Iwata et al., 2001).

Despite advances in our understanding of the role of APP processing in AD, the normal physiological function of this protein has proven more difficult to elucidate (De Strooper and Annaert, 2000). Initial reports speculated that the protein is a cell-surface receptor (Kang et al., 1987). The discovery of interacting proteins, genetic studies in animals, and gene expression profiling have since led to the identification of putative pathways for the APP family associated with cellular and developmental changes.

**Knockouts, knockdowns and transgenics**

Clues to physiological functions of the APP family mentioned above come from knockout phenotypes in different organisms. Loss of one copy of the APP orthologue APL-1 in *Caenorhabditis elegans* leads to pharyngeal pumping defects (Zambrano et al., 2002), while loss of both copies leads to larval lethality (Hornsten et al., 2007; Zambrano et al., 2002). This lethality can be rescued by pan-neuronal expression of the apl-1 ectodomain, which indicates that APP plays a non-cell-autonomous role in development (Horsten et al., 2007). In *Drosophila*, deletion of the single APP-like gene (Appl) results in only subtle behavioral defects that can be rescued by wild-type but not mutant APL or APP (Luo et al., 1992), but a later study suggested that deletion and mutation affects kinesin-mediated axonal transport and neuronal viability (Gunawardena and Goldstein, 2001).

In mice, single knockouts of APP gene family members are viable. However, APP knockout mice display several phenotypes, which include impairment in spatial learning and long-term potentiation (LTP). These deficits can be rescued by a knock-in allele of sAPP-α, indicating that the ectodomain of APP is sufficient for APP function in the adult brain (Ring et al., 2007). By contrast, the APP-APLP2 and APLP1-APLP2 double knockout or APP-APLP1-APLP2 triple knockout result in loss of viability. APP-APLP2 double knockout mice have a neuromuscular junction defect (Wang et al., 2005), whereas the triple knockout has neuronal ectopias resembling type II lissencephaly (Herms et al., 2004). These findings demonstrated the importance of the APP family in development, and suggest functional redundancy consistent with a role in neuronal cell adhesion and migration. Interestingly, knocking out Fe65, an intracellular APP-interacting protein, in worms (Zambrano et al., 2002) or the combined Fe65-Fe65L1 knockout in mice (Guénette et al., 2006) results in phenotypes strikingly similar to those seen when APP genes are knocked out. This suggests that these proteins are functionally as well as physically connected (see below).

**APP-transgenic animals provide further clues to potential physiological roles.** Overexpression of APP family members in *Drosophila* affects development of the peripheral nervous system, and genetic analyses indicate Notch gain-of-function phenotypes may be due to interaction of APP with Numb, a negative regulator of Notch signaling (Merdes et al., 2004). Other reports suggest that APP and Notch interact directly through their transmembrane domains (Chen et al., 2006; Fassa et al., 2005; Oh et al., 2005). Transgenic APP flies also show increased axonal arborization, which critically depends on the cytosolic domain and its interaction with Abl kinase (Leyssen et al., 2005).

Brain injury induces APP expression, which suggests that APP plays a repair role in this context. The correlation of AD with head trauma may reflect an increase in APP expression, with Aβ generation being an unfortunate epiphenomenon. **APP-transgenic mice have been generated in the hope of reproducing the Aβ-containing plaques of AD and testing therapeutic candidates.** A recent report shows that pathological, physiological and behavioral deficits in APP-transgenic mice are not seen in those with a mutation at a caspase-cleavage site in the intracellular domain (Galvan et al., 2006) and yet still produce Aβ and amyloid deposits. This suggests a role for the APP intracellular domain and possibly for the caspase-released cytosolic tail in the pathogenesis of AD.

**APP as a putative receptor**

The idea that APP functions as a receptor was bolstered by the discovery that the Notch receptor signals through proteolytic processing that is remarkably similar to that of APP (Annaert and De Strooper, 1999; Selkoe and Kopan, 2003). Notch is essential for many differentiation events during development and adulthood. Signaling is initiated by interaction with cognate ligands, which triggers shedding of the Notch ectodomain by ADAM10 and ADAM17. These metalloproteases also shed the ectodomain of APP through the α-secretase pathway (Buxbaum et al., 1998; Lammich et al., 1999). Interestingly, the ADAM17-mediated shedding of APP can be stimulated by phorbol esters and other means of activating protein kinase C (Buxbaum et al., 1993).

The membrane-associated stub of Notch that remains is then cut by γ-secretase (De Strooper et al., 1999), releasing an intracellular domain that translocates to the nucleus and interacts with certain transcription factors to control gene expression and cell fate. Thus, the thinking was that APP may likewise have extracellular ligands and that the intracellular domain (AICD) might translocate to the nucleus (Cupers et al., 2001) and interact with factors regulating the expression of certain genes. Alternatively, APP proteolysis may be a mechanism for turning off normal APP functions. In this regard, the proteases are simply degradative, a concept that is especially true for γ-secretase, which cleaves many type I integral membrane proteins and has even been likened to a proteosome of the membrane (Kopan and Ilagan, 2004).

The search for APP ligands has not been especially fruitful. F-spondin, a secreted neuronal protein purportedly involved in cell-cell interactions, was identified by affinity isolation, and coexpression of this protein prevents shedding of the APP ectodomain by β-secretase and reduces Aβ production (Ho and Sudhof, 2004). However, it is unclear whether soluble F-spondin added to cultures has the same effect, or whether the F-spondin–APP interaction occurs when the two proteins are expressed in different cells. Reelin, an extracellular matrix protein essential for cortical development that shares homology with F-spondin, was shown to...
increase binding of the reelin signaling mediator Dab1 to APP (Hoe et al., 2006b). Furthermore, fewer reelin-expressing pyramidal neurons are observed in the entorhinal cortex of APP-transgenic mice and AD brains (Chin et al., 2007). The Nogo-66 receptor, implicated in axonal sprouting in the adult CNS, has also been reported to interact with the APP ectodomain and inhibit Aβ production (Park et al., 2006). LRP and SORL1 (SORLA, LR11) also bind to the APP ectodomain and influence Aβ production (Andersen et al., 2005; Bu et al., 2006). Indirect triggering of β- and γ-secretase cleavage of APP has been reported for platelet-derived growth factor receptor Abl, and as mentioned above, activation of protein kinase C leads to APP proteolysis through the α-secretase pathway (Buxbaum et al., 1993).

sAPP released from the membrane may serve as a signaling molecule. Evidence suggests that the shed ectodomain plays a role in the growth of fibroblasts in culture (Park et al., 2006). sAPP was found to be neuroprotective for primary neurons in culture, preventing elevations in intracellular Ca²⁺ levels caused by glucose deprivation and raising the excitotoxic threshold of glutamate (Mattson et al., 1993), as well as mediating axonal and dendritic growth (Perez et al., 1997).

APP may also serve as an adhesion molecule: it binds to extracellular matrix proteins such as heparin and collagen (Beher et al., 1996; Multhaup, 1994). Homo- and heterodimerization between the APP family members in adjacent cells has also been suggested to promote intercellular adhesion (Soba et al., 2005). Such a mechanism would be analogous to that of known cell adhesion molecules such as cadherins and nectins. APP and Fe65 have been reported to influence cell motility, and several regulators of actin dynamics were recently found to be regulated by AICD (Guénette et al., 2006; Muller et al., 2007; Sabo et al., 2001; Sabo et al., 2003).

**Intracellular interactors**

Numerous proteins that interact with the intracellular tail of APP have been identified. These include proteins that are known to play a role in vesicular or protein trafficking: X11 (Mint1) and X11L (Mint2) involved in vesicle exocytosis; Jun N-terminal-kinase-interacting protein 1 (JIP-1), a scaffold protein that binds kinesin light chain 1 and coordinates transport of phosphorylated APP into neurites; kinesin 1; Pat1α, a microtubule-interacting protein that plays a role in anterograde transport of APP and APLPs; and autosomal recessive hypercholesteremia (ARH) protein, an adaptor protein involved in the internalization of LDL receptors (Kamal et al., 2000; King et al., 2004; Kuan et al., 2006; Muresan and Muresan, 2005; Zheng et al., 1998; Noviello et al., 2003).

APP-binding proteins are also involved in brain development: the Fe65 proteins transmit an APP-dependent signal important for neuronal positioning in the developing cortex; mDab1 plays a key role in reelin signaling in the developing cortex; and Numb is a scaffold protein important for Notch signaling (Guénette et al., 2006; Hoe et al., 2006b; Roncarati et al., 2002). Other APP-tail-binding proteins are implicated in regulating cell cycle progression; these include Gα, PAK3, APP-BP1 (Chen et al., 2007; Chen et al., 2003; Giambarella et al., 1997; McPhie et al., 2003). In the case of Gα and PAK3, this has been associated with FAD-linked APP mutations. Interaction of the APP tail with Shc and Grb2 is thought to lead to signaling through the Ras-Raf-MAPK pathway, and APP-Shc-Grb2 complexes have been reported to be increased in AD patients (Russo et al., 2005).

The APP C-terminus is a substrate for several enzymes. Proteolysis by the γ-secretase complex occurs within the 99-residue C-terminal tail of APP, and binding to presenilins by this APP stub has been demonstrated. Phosphorylation of the intracellular tail is mediated by several kinases. These include the Ser/Thr kinases JNK, CDK5, GSK-3β, which phosphorylate Thr668, and the non-receptor tyrosine kinases Abl and Src, and nerve growth factor tyrosine-kinase receptor A (TrkA), which phosphorylate Tyr682 (Russo et al., 2005). Phosphorylation has been shown to regulate which proteins bind to the APP tail. JNK phosphorylation leads to preferential binding to JIP-1, whereas JIP-2 binds to phosphorylated and unphosphorylated APP equally well (Muresan and Muresan, 2005). A Glu substitution at Thr668, mimicking phosphorylation, destabilizes the Fe65-APP interaction (Ando et al., 2001), whereas Tyr682 phosphorylation facilitates binding of Shc and Grb2 to APP (Russo et al., 2005).

A recent study shows binding of the APP tail to hARD1, an acetylase subunit, but modification of the APP tail by this acetylase has not been examined (Asaumi et al., 2005). In addition, prolyl isomerases, Pin1 and FKB12, bind to the APP C-terminus. Pin1 binds Thr68 phosphorlated APP and accelerates its isomerization (Pastorino et al., 2006).

There are numerous reports addressing the impact of APP-binding proteins on APP proteolysis and Aβ generation (Russo et al., 2005). In the case of Fe65 and Dab1, the effects are cell type dependent, possibly owing to the existing complement of competing cellular APP-binding proteins in each cell type (Hoe et al., 2006a; Hoe et al., 2006b; Parisiadou and Efthimiopoulos, 2007). In addition, tripartite complexes involving APP-binding proteins, APP and other molecules, such as aldehydein-X11L-APP and LRP-Fe65-APP, have been shown to influence Aβ generation (Araki et al., 2004; Yoon et al., 2005).

The APP-interacting protein that has generated the most interest is Fe65, because a ternary complex consisting of Fe65, APP and the histone acetyltransferase Tip60 has been shown to activate transcription (Baek et al., 2002; Cao and Sudhof, 2001; Cao and Sudhof, 2004). Most of the evidence supporting a role for an APP-Fe65-Tip60 complex in transcriptional activation comes from studies using an artificial reporter system in cells overexpressing APP or AICD. Although AICD is rapidly degraded by IDE (Edbauer et al., 2002), it can be detected in primary neurons during differentiation in culture (Kimberly et al., 2005). Nuclear translocation of Fe65 is required for transactivation, and γ-secretase-mediated cleavage of APP can facilitate this event. However, one report shows APP-Fe65-Tip60 signaling occurring independently of γ-secretase cleavage (Hass and Yankner, 2005). Moreover, Fe65-GAL4 expression alone was recently shown to mediate
transcriptional activation of the reporter, which could be partly blocked by knocking down APP or overexpressing Tip60 (Yang et al., 2006).

Intracellular and extracellular factors that regulate Fe65-APP-dependent transactivation have also been identified. 14-3-3y can bind both APP and Fe65 and facilitate transcriptional activation (Sumioka et al., 2005). 17-β estradiol was reported to repress transcriptional activation through sequestration of Fe65 away from the Cda82 (KAI-1) promoter through increased binding of estrogen receptor α and Fe65 (Bao et al., 2007). Candidate AICD-target genes have been suggested (e.g. tetraspanin CD82, APP, GSK3β and nephrilysin), although one report provides evidence that the expression of none of these is γ-secretase dependent and that Fe65 has a weak stimulating effect on various promoters (Hebert et al., 2006). Several novel AICD-regulated candidate genes have been identified as regulators of actin dynamics; however, a direct association of Fe65 or AICD with their promoters remains to be demonstrated (Muller et al., 2007). Thus, although the APP-Fe65 interaction is probably physiological, the identity of downstream effectors remains unclear. In a very recent study, the EGFR promoter was identified as a target for AICD and Fe65 in mouse brain and embryonic fibroblasts. Binding of AICD and Fe65 to the EGFR promoter represses EGFR transcription (Zhang et al., 2007).

AICD has also been implicated in regulating phosphoinositide-mediated Ca2+ signaling (Leissring et al., 2002). Presenilin and γ-secretase activity were crucial to this process, which involves release of endoplasmic reticulum Ca2+ stores. Cells lacking APP show deficits in Ca2+ signaling that can be rescued by stores. Cells lacking APP show deficits that regulate Fe65-APP-dependent Tip60 (Yang et al., 2006).

Conclusions
Our understanding of the normal functions of APP remains limited. This integral membrane protein is reminiscent of a receptor and is processed in a manner closely similar to the Notch family of receptors. Certain factors can indirectly trigger APP proteolysis; however, no extracellular ligand for APP has been identified, and no downstream target genes have been confirmed. Some proteins that interact with the ectodomain portion of APP can inhibit proteolysis, whereas the identities of others suggest APP functions as an adhesion molecule. Dimerization within the APP family may mediate an adhesion role, whereas interaction with the Notch pathway may modulate Notch signaling. Evidence for an APP signaling function comes from studies with Fe65 and Tip60 and with proteins that play a role in established signal transduction pathways. Kinases may play a key role in regulating the stability of APP; its interaction with intracellular partners and downstream signaling events. Much work needs to be done to close the large gaps in our knowledge about APP biology.

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