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A putative role of the Amyloid Precursor Protein Intracellular Domain (AICD) in transcription

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Amyloid Precursor Protein (APP) Intracellular Domain (AICD) is the product of APP processing realized by α- or β-secretases and γ-secretase. It was shown that AICD is able to interact with several proteins which regulate its stability and cellular localization. The Fe65 adaptor protein translocates AICD into nucleus where the APP-Fe65-Tip60 ternary complex may activate transcription of target genes. In the light of recent studies AICD seems to be another product of APP proteolysis endowed with important biological functions that may contribute to Alzheimer's disease pathology.

Key words: Amyloid Precursor Protein (APP), Amyloid Precursor Protein Intracellular Domain (AICD), Fe65, Tip60, adaptor protein, transcription activation

INTRODUCTION

The original report by Glenner and Wong (1984) that a 4.2 kDa β-amyloid (Aβ) peptide (originally termed "beta protein") is the main component of senile plaques, found *post mortem* in brains of Alzheimer's disease (AD) patients, has been a real boost for the molecular research on AD. Soon, the cDNA for a putative 695 aa Aβ precursor protein (APP) was identified and then the protein itself, a single-span membrane receptor with a large extracellular domain, of which Aβ appeared to be just a small midsection (Kang et al. 1987). APP is a member of a conserved family of type I membrane proteins which in mammals includes also APP like protein 1 (APLP1) and 2 (APLP2). APP and APLP2 are ubiquitous with high expression in neurons while APLP1 is brain-specific. Far from being just a source of the troublemaking sticky Aβ peptide the APP protein is an important cell constituent that may play a role in the recognition of extracellular signals, cell adhesion and apoptosis. In neurons APP is required for synaptogenesis, synapse remodeling and neurite outgrowth (reviewed in Zheng and Koo 2006). APP expression is increased during neuronal maturation and differentiation (Hung et al. 1992) and during traumatic brain injury (Ciallella et al. 2002). Conforming to its putative role in these vital cellular processes APP/APLP1/APLP2 knockout (KO) appeared to be lethal (Heber et al. 2000). APP KO mice are viable and show memory loss, but without general neuron loss (Phinney et al. 1999).

It was only natural that the main scientific interest concentrated on APP proteolytic processing that generates the malefic Aβ. After an intense research it led to the identification of a novel intramembrane proteolytic machinery termed the γ-secretase complex (reviewed in Kimberly and Wolfe 2003, Żekanowski et al. 2004). Numerous mutations in both APP and γ-secretase which correlate with early onset AD symptoms were identified and strengthened the causal link between these proteins and AD pathology. Only recently attention was turned to yet another product of APP prote-

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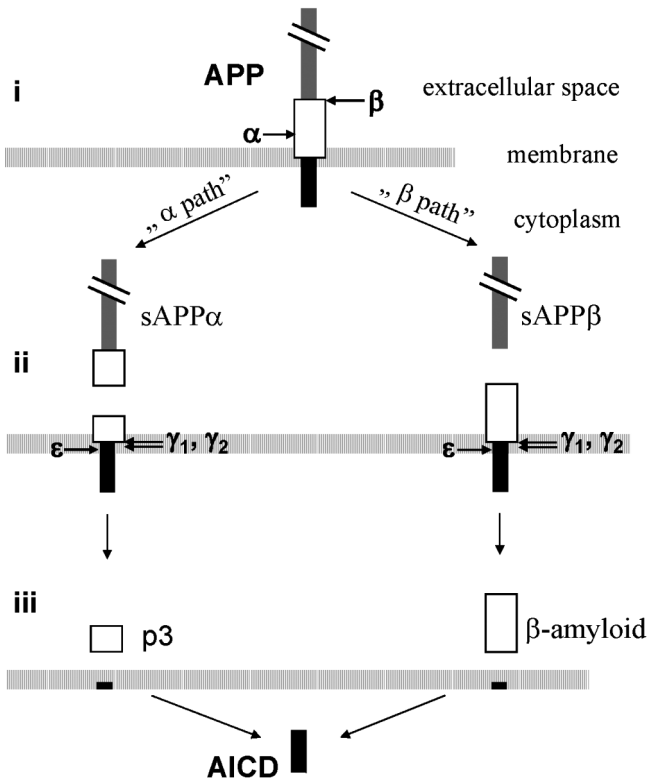

Fig. 1. Proteolytic processing of APP. The first cleavage is realized in APP extracellular domain by α- or β-secretase activity (i) and releases soluble N-terminal fragments sAPPα or sAPPβ. Thereafter γ-secretase generates p3 or β-amyloid (40-42) (ii) as a result of intramembrane digestion. Simultaneously, in both cases, the C-terminal fragment called APP Intracellular Domain (AICD) is released into cytoplasm (iii).

olysis, termed AICD (APP Intracellular Domain), which represents its cytoplasmic C-terminal fragment (Fig. 1). This review is devoted to AICD, its binding partners, its putative role in transcription and implications of its activity for AD pathology.

GENERATION OF AICD

Similarly to many other membrane receptors the full-length APP is a subject to ectodomain shedding, due to regulated intramembrane proteolysis (RIP). Paradoxically, and in contrast with other receptors, the primary signal initiating APP proteolysis remains unknown. The first cleavage is performed by either α- or β-secretase that release large soluble N-terminal fragments, sAPPα or sAPPβ, into the extracellular/luminal space and leave a membrane-tethered 83- or 99 aminoacid C-terminal remnants, respectively (Fig.1). The best documented candidates for α-secretase activity are proteases of the ADAM (a desintegrin and metalloproteinase) family, namely ADAM10 and ADAM17, while the splitting at the β-site is effectuated by BACE1 (β-site APP cleaving enzyme) (reviewed in Esler and Wolfe 2001). Thereafter a second cleavage is realized in the intramembrane region by γ-secretase which, depending on where the first cleavage occurred, releases either the p3 fragment or Aβ. γ-secretase is an intramembranous multimeric complex the proteolytic activity of which is confined to presenilin 1 (PS1) or 2 (PS2) (Kimberly and Wolfe 2003). This activity seems to be largely nonselective, occurring in at least 3 different sites: V636, A638 and L645 (ε-cleavage site) of the APP molecule (Figs 1 and 2) (Sastre et al. 2001, Yu et al. 2001). The resulting main products are Aβ40 or Aβ42, the latter considered to be more amyloidogenic, and an intracellular 50 aa long C-terminal domain (AICD) (Figs 1 and 2). In contrast to its ill-famed counterpart the existence of AICD remained elusive until its presence was first documented in guinea pig brain (Pinnix et al. 2001). Additional cleavage by caspase-3 between D664 and A665 may render a 31 aa C-terminal fragment (CTF) (Fig. 2) (Gervais et al. 1999). AICD is extremely labile and can be further degraded by the insulin degrading enzyme (Edbauer et al. 2002) or proteasome (Nunan et al. 2001). The generation of AICD, like that of Aβ, takes place in membrane compartments upstream of ER and is dependent upon presenilins (Bergman et al. 2003).

Both the topography of the ε-cleavage site in APP and the involvement of presenilins are reminiscent of the processing of another class I membrane receptor, Notch, a core component of a well established signaling pathway (reviewed in Selkoe and Kopan 2003). Notch processing starts after its interaction with ligands (Delta and Serrate/Jagged), which themselves are integral membrane proteins, initiating a signal cascade that determines cell fate in developmental processes. The signal cascade involves Notch intracellular domain (NICD), which is released by presenilin cleavage and subsequently migrates to the cell nucleus to become a component of a transcriptional complex. These similarities prompted researchers to investigate a putative role of AICD in transcription.

AICD BINDING PARTNERS

The C-terminal intracellular APP domain contains at least three functionally important motifs enabling

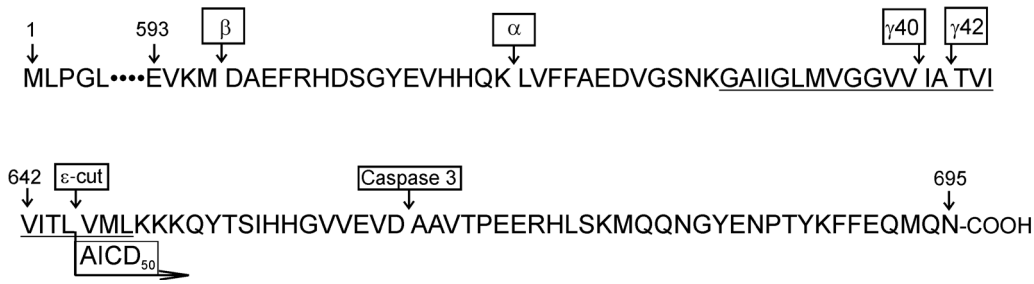

Fig. 2. The aminoacid sequence of the 569-695 C-terminal APP fragment (695 aa APP isoform). Underlined aminoacids form APP transmembrane domain. β, α, γ40, γ42 and ε symbols correspond to secretase cleavage sites. Caspase cleavage site generating a 31 aa CTF is also indicated. The only *in vivo* detected form of AICD is the ε-cleaved 50 aa AICD (Sastre et al. 2001), however, 57 and 59 aa AICD (corresponding to the γ-cleavage sites) are often used in *in vitro* experiments.

APP (and AICD) interaction with several binding partners (Fig. 3). The highly conserved 682-YENPTY-687 motif is recognized by proteins containing phosphotyrosine interaction domains (PID). These are proteins of the Fe65 family (Fe65, Fe65L1 and Fe65L2) (Fiore et al. 1995), the Jip (c-Jun N-terminal kinase interacting protein) family (Jip1b and Jip2) (Matsuda et al. 2001, Scheinfeld et al. 2002), the X11 family (X11, X11L and X11L2) (Borg et al. 1996), the Shc family (Shc A and Shc C) (Tarr et al. 2002) as well as mDab1 (mammalian disabled-1) (Howell et al. 1999), Numb and Numb-like proteins (Roncarati et al. 2002), KLC (kinesin light chain) (Kamal et al. 2000), Abl – non-receptor tyrosine kinase (Zambrano et al. 2001) and clathrin (Marquez-Sterling et al. 1997) (Fig. 3). On the other hand, the 14-3-3γ protein which is highly expressed in brain, skeletal muscle and heart (Horie et al. 1999) binds to the 667-VTPEER-672 motif of APP/AICD while PAT1 (protein interacting with APP tail 1), a microtubule-interacting protein, binds to the 653-YTSI-656 motif (Zheng et al. 1998) (Fig. 3). The available experimental data suggest that these interactions may influence exocytosis and processing of APP. In this regard interaction with PAT1 seems to regulate basolateral sorting of APP while binding of X11α prolongs its half-life and inhibits generation of Aβ probably by retarding exocytosis (Mueller et al. 2000). On the other hand Fe65 promotes APP translocation to the plasma membrane and its processing (Sabo et al. 1999), although this effect may be cell type dependent (Ando et al. 2001). Overexpression of 14-3-3γ, which interacts with both APP and Fe65, seems to have no apparent effect on APP processing (Sumioka et al. 2005).

PHOSPHORYLATION OF AICD

The AICD sequence contains eight potential phosphorylation sites. Seven of them (Y653, S655, T668, S675, Y682, T686 and Y687) were found to be phosphorylated in APP from brains of AD patients (Lee et al. 2003). Being often located in the protein interaction sites (Fig. 3), the phosphorylatable residues may interfere with protein binding, and in turn, with APP/AICD function. Phosphorylation of Y682 was shown to enhance Abl (Zambrano et al. 2001) and Shc binding (Tarr et al. 2002), while at the same time it may interfere with Fe65, X11 and mDab1 binding (Zambrano et al. 2001). A constitutive phosphorylation of the T668 residue is observed specifically in the brain and seems to be a critical phosphorylation site determining AICD destiny (Iijima et al. 2000). When phosphorylated, T668 blocked the interaction of AICD and APP with

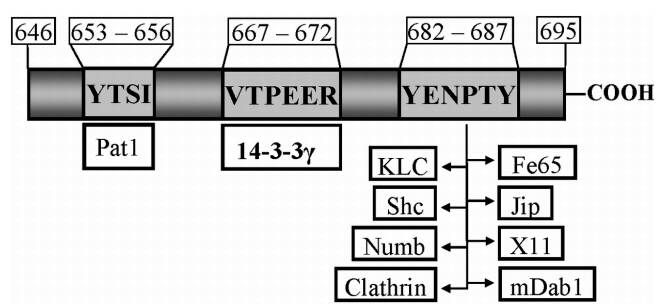

Fig. 3. APP/AICD motifs responsible for interaction with its binding partners. 653-YTSI-656 motif binds PAT1; 667-VTPEER-672 motif binds 14-3-3γ; 682-YENPTY-687 motif binds proteins from the Fe65 family (Fe65, Fe65L1), X11 family (X11α, X11L, X11L2), Jip family (Jip1b, Jip2) as well as the mDab, Shc, Numb, KLC proteins and clathrin.

14-3-3γ (Sumioka et al. 2005). On the other hand, phosphorylation at this site is indispensable for Fe65 binding and hence for AICD transcriptional activity (see below) (Chang et al. 2006). The level of T668 phosphorylation correlates with neurite outgrowth in PC12 cells and impacts hippocampal plasticity (Ando et al. 1999).

NUCLEAR TRANSLOCATION OF AICD

The interaction between APP/AICD and Fe65 has received the greatest attention. Fe65 seems to be a scaffolding/adaptor protein, as reflected by its multi-domain structure and multiple binding partners. It possesses three putative protein-protein interaction domains: one WW domain and two PID domains. It was proposed to be involved in cytoskeleton remodeling and cell motility (Sabo et al. 2001), as well as in gene regulation. Minopoli and coworkers (2001) showed that Fe65 can be also found in the nucleus and that APP acts as an extranuclear anchor for Fe65 and prevents its nuclear translocation. On the other hand, once APP is cleaved, the Fe65 adaptor protein rescues the resultant AICD from rapid degradation (Kimberly et al. 2001). Fe65 seems to be essential for the nuclear translocation of AICD and AICD mutated at the Fe65 interaction site remains largely cytosolic (Kimberly et al. 2001, Kinoshita et al. 2002a). In contrast to Fe65, the X11α adaptor protein arrests AICD within the cytosol (von Rotz et al. 2004). Cao and Sudhoff (2001) first showed, by means of yeast two-hybrid method and GST-pull down assay, that FE65 also associates with a histone acetyltransferase, TIP60, and that both these proteins colocalize with AICD in the nucleus. A ternary complex consisting of AICD, Fe65 and Tip60 was observed in spherical nuclear spots of HEK293 cells (von Rotz et al. 2004) suggesting its co-localization with sites of active transcription. Tip60 was earlier described as a component of a multimeric protein complex containing histone acetylotransferase, ATPase, DNA helicase and structural DNA binding activity (Ikura et al. 2000). Other authors found that Fe65 could also interact with the CP2 (CP2/LSF/LBP1) transcription factor (Zambrano et al. 1998). The involvement of AICD in the complex was confirmed by showing that AICD co-immunoprecipitated with CP2 in the presence of Fe65 (Kim et al. 2003). Altogether these results suggest that AICD, *via* its association with the Fe65 adaptor protein, may be a constituent of a multimeric complex consisting of proteins with transcription-related activities (Fig. 4). Thus, the NICD-inspired concept that AICD may regulate transcription began to take shape and awaited functional verification.

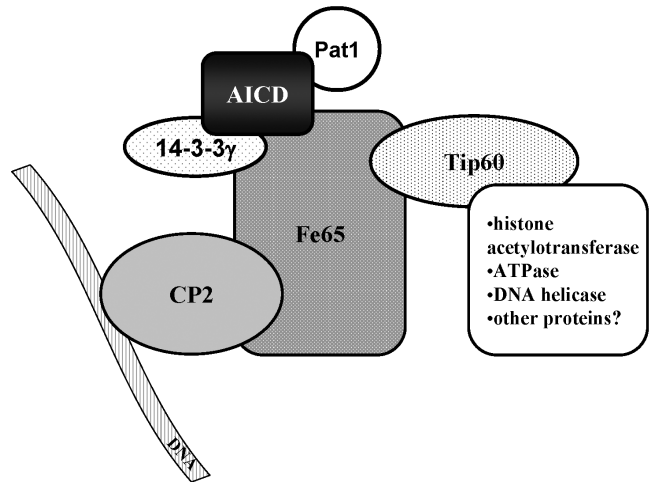

Fig. 4. Schematic representation of the transcriptional protein complex containing AICD

AICD MEDIATED GENE TRANSCRIPTION

In a pioneer experiment designed to investigate the putative involvement of AICD in transcription Cao and Sudhof (2001) used a fusion protein consisting of the DNA-binding domain of the yeast Gal4 (or bacterial LexA) transcription factor and the C-terminal APP domain and showed that such protein could activate transcription from the Gal4- or LexA-dependent reporter plasmid, albeit to a small extent. Interestingly, cotransfection with the Fe65 protein highly elevated reporter gene activity when assayed in several cell types. Moreover, mutation within the Fe65 binding site abolished transcriptional activation mediated by the C-terminal domain of APP (Cao and Sudhof 2001). TIP60, a histone acetylotransferase identified as a binding partner of Fe65, did not show transactivation ability when assayed as a Gal4-fusion protein but appeared to act as a co-activator for the AICD-Fe65 complex. A simultaneous co-expression of APP (or AICD), Fe65 and Gal4-Tip60 led to dramatically enhanced expression of the reporter gene (over 100 times) while the presence of CP2, a transcription factor interacting with Fe65, had no effect. These results indicate that the AICD-Fe65-Tip60 triplet may play a role in activating

gene transcription (Cao and Sudhof 2001). An alternative model was proposed in which the C-terminal part of APP is required only to activate Fe65 in a membrane-dependent process making AICD nuclear translocation dispensable for the observed transcription activation (Cao and Sudhof 2004).

The Gal4 experimental system proved to be also helpful in examining the potential role of other APP/AICD binding proteins in transcriptional activation. Jip1b overexpression increased transcriptional activation mediated by the Gal4-fused APP or AICD (Sheinfeld et al. 2003). Overexpression of 14-3-3γ with Gal4-AICD fusion protein enhanced the FE65 dependent gene transactivation two-fold in mouse neuroblastoma-2a cells (Sumioka et al. 2005). Inversely, X11α, which trapped AICD in the cytoplasm displayed an inhibitory function in AICD-mediated gene transactivation (Biederer et al. 2002).

The results obtained employing Gal4-fusion proteins were soon followed by those derived from more physiological experimental setups. Overexpression of AICD in PC12 cells and primary rat neurons transfected with a vector encoding luciferase under the control of the human GSK-3β (glycogen synthase kinase-3β) gene promoter increased the promoter activity more than fivefold (Kim et al. 2003). Furthermore, AICD overexpression resulted in a higher level of GSK-3β protein and mRNA in these cells. When PC12 cells and rat primary cortical neurons were transfected with APP bearing a mutation that facilitates cleavage by γ-secretase (Swe-APP), higher GSK-3β and higher tau phosphorylation levels were observed (Kim et al. 2003). These findings directly implicated AICD in regulation of expression of an enzyme playing a key role in the pathogenesis of Alzheimer's disease, Huntington's disease and bipolar disorder (Jope and Johnson 2004), as well as in metabolic disorders such as type II diabetes (Eldar-Finkelman 2002). Moreover, these results strongly suggest that the elevation in GSK-3β gene promoter activity is mediated by the CP2 transcription factor, since mutation within a proximal CP2 binding site in the GSK-3β promoter abolished its activation (Kim et al. 2003). Accordingly, CP2 may be a candidate transcription factor responsible for anchoring the hypothetical transcriptional complex, whose core would consist of AICD, Fe65 and Tip60, to defined nucleotide sequences on target gene promoters (Fig. 4).

The KAI1 gene described as "metastasis suppressor gene", encoding a transmembrane protein whose decreased level in many tumors is correlated with malignance grade and metastatic abilities (White et al. 1998), was also shown to be AICD target by means of the luciferase assay (Baek et al. 2002). Again, mutation within the Fe65 binding sequence abolished transcriptional activation. The involvement of AICD in KAI1 gene activation was further supported by documentation of the actual binding of AICD, Tip60 and Fe65 to the KAI1 gene promoter (Baek et al. 2002). This complex had the ability of displacing the N-CoR repressive complex from the KAI1 promoter. Other researchers delivered evidence that the estrogen receptor alfa (ERα) can bind to Fe65 associated with AICD on the KAI1 gene promoter and change the complex into a repressive one (Bao et al. 2007). Accordingly, β-estradiol was able to inhibit AICD-mediated promoter activation. AICD was also shown, together with TIP60 and Fe65, to stimulate the activity of the neprilysin gene promoter and to increase the level of this protein in HEK293 cells (Pardossi-Piquard et al. 2005). Furthermore, the level of neprilysin appeared to be reduced in PS-deficient cells. Since neprilysin is an enzyme capable of degrading Aβ, the existence of an autoregulatory loop was suggested (Pardossi-Piquard et al. 2005). RT-PCR, performed on RNA from AICD-overexpressing cells, showed increased mRNA levels for KAI1, GSK-3β, APP, BACE and TIP60 (von Rotz et al. 2004), while results from APP–overexpressing transgenic mice, beside a higher KAI1 expression, also revealed increased level of TIP60 and Fe65 (Baek et al. 2002) thus considerably prolonging the list of putative AICD targets. As with neprilysin, the results on APP and BACE may suggest an involvement of AICD in a positive feedback mechanism (von Rotz et al. 2004).

These findings were challenged by studies performed by Hebert and coworkers (Hebert et al. 2006) who showed that pharmacological inhibition of APP proteolysis (inhibition of AICD generation) in several cell lines did not result in clear differences in the protein or/and mRNA level of the putative AICD regulated genes, namely KAI1, GSK-3β, APP and neprilysin. No differences in the level of these proteins were noticed between control and APP/APPL2 double KO mouse embryonal fibroblasts or in γ-secretase–deficient (PS double KO) mice. On the other hand the authors confirmed that AICD overexpression was able to increase KAI1 gene promoter activity in a luciferase assay.

Muller and coworkers employing microarray analysis reported no changes in transcription level of GSK-3β or KAI1 in Tet2 human neuroblastoma cells overexpressing AICD or in the frontal cortex of AD patients (Muller et al. 2007). On the other hand, the same analysis comparing AICD and/or Fe65 overexpressing cells versus control cells showed an increased level of eight genes. Three of them are involved in the regulation of the cytoskeleton: transgelin, α2-actin and tropomyosin 1. The latter one originally described as a protein interacting with actin filaments of myofibrils is found in neurofibrillary tangles, which are the intraneuronal hallmarks of AD (Galloway et al. 1990). Other genes whose expression was increased by AICD/Fe65 were: flavoprotein oxidoreductase (MICAL2), Ras-associated protein (RAB3B), fibronectin 1, insulin growth factor binding protein 3 (IGFBP3), solute carrier family 7 and member 5 (SLC7A5) (Muller et al. 2007). Further verification of *in vitro* results came from the work of Ryan and Pimplikar (2005) who constructed AICD/Fe65 overexpressing mice. Those mice displayed twofold elevated KAI1 expression level in total brain mRNA in comparison to control animals. However, cytosol brain extracts did not display any changes in the GSK-3β protein level although the extent of Ser9 phosphorylation was reduced which correlated with higher GSK-3β enzymatic activity (Ryan and Pimplikar 2005)

The net effect of AICD on gene expression is thus still controversial. As mentioned above its involvement in a complex containing *bona fide* transcriptional activators is well established and its presence on actively transcribed gene promoters has been documented (Baek et al. 2002, Bao et al. 2007). On the other hand, studies on PS-deficient cells, transgenic animals or microarray results do not always show changes in the expression of the putative AICD targets that would correspond to the level of transcription activation observed in the *in vitro* studies. It should be stressed that the pronounced changes observed *in vitro* were evoked by a very high level of AICD unlikely to exist *in vivo* where, adding to AICD instability, its effect on transcription can be largely counteracted by other mechanisms or fine-tuned to avoid pathological outcomes. It could be argued though that the transcriptional potential of AICD and its partners may take its toll in a longer time range and/or when the cleavage of APP is augmented as in FAD cases or when the control mechanisms become inactive.

GSK-3β AS THE PUTATIVE LINK BETWEEN AICD AND AD-PHENOTYPE

Pathological hallmarks of AD include extracellular senile plaques containing Aβ and intraneuronal tau protein-rich neurofibrillary tangles (NFTs) together with a widespread neuronal cell death and astrocytosis. The question thus arises if, how and to what extent AICD transcriptional activity may contribute to AD symptoms. Ectopic expression of AICD invariably led to increased apoptosis of rat pheocytoma cells and cortical neurons (Kim et al. 2003) and of human neuroglioma H4 cells (Kinoshita et al. 2002b). The apoptotic effect was not observed if AICD nuclear translocation was prevented. AICD mutants that did not bind FE65 were less toxic (Kim et al. 2003). Further studies, showing that mutant TIP60 attenuated the apoptotic effect of AICD (Kinoshita et al. 2002b) while sodium butyrate, an inhibitor of histone deacetylation, potentiated it (Kim et al. 2004) firmly linked the detrimental effect of AICD overexpression to its activity in transcription. The most probable AICD transcriptional target that could mediate these effects seems to be GSK-3β. GSK-3β is one of several isoforms of the serine/threonine kinase, which was initially identified as the enzyme involved in glycogen metabolism. It is highly expressed in the central nervous system and phosphorylates many cytosolic proteins, most importantly the tau protein which, in its hyperphosphorylated state, becomes the main component of NFTs (Lovestone et al. 1994). Studies on transgenic mice overexpressing GSK-3β in the cortex and hippocampus showed that such animals have more hyperphosphorylated tau protein which tends to form aberrant aggregates characteristic of AD (Lucas et al. 2001). Furthermore, more apoptotic cells were found in dentate gyrus of the transgenic animals compared with control ones. Mice overexpressing GSK-3β also developed symptoms of reactive astrocytosis (Lucas et al. 2001). In other words, GSK-3β overexpression in mice brain recapitulated the main AD symptoms which could be reversed when GSK-3β activity was switched off (Engel et al. 2006). Taking into account that GSK-3β was also shown to mediate Aβ toxicity (Sun et al. 2002) the central role of this enzyme in AD pathology becomes obvious. As mentioned before, real-time PCR results suggest that AICD may also directly increase APP level and activate its cleavage (von Rotz et al. 2004). Furthermore, AD pathology has been often linked with

disturbed calcium homeostasis. In this respect, it was suggested that AICD may regulate phosphoinositide-mediated calcium signaling (Leissring et al. 2002).

CONCLUSIONS

Recent data strongly suggest that Aβ is not the sole product of the APP processing that may play a role in development of AD. Results obtained by means of the Gal4 yeast transcription factor system as well as in other *in vitro* and *in vivo* assays provide strong evidence of AICD-mediated transcription activation. This activity, reminiscent of NICD, is effectuated *via* complicated AICD trafficking and complex formation with proteins possessing transcription-related activities. Interestingly, transcription of the GSK-3β gene, coding for an enzyme strongly implicated in AD phenotype formation, is activated by AICD. Furthermore, AICD-mediated elevation of APP and BACE (β-secretase) expression suggests the involvement of AICD in an autostimulatory loop with potential cell-detrimental effects. Although speculations and contradictory results abound, it is likely that AICD represents an important AD phenotype-contributing factor.

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