Amyloid Precursor Protein (APP) Metabolites APP Intracellular Fragment (AICD), Aβ42, and Tau in Nuclear Roles*

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Amyloid precursor protein (APP) metabolites (amyloid-β (Aβ) peptides) and Tau are the main components of senile plaques and neurofibrillary tangles, the two histopathological hallmarks of Alzheimer disease. Consequently, intense research has focused upon deciphering their physiological roles to understand their altered state in Alzheimer disease pathophysiology. Recently, the impact of APP metabolites (APP intracellular fragment (AICD) and Aβ) and Tau on the nucleus has emerged as an important, new topic. Here we discuss (i) how AICD, Aβ, and Tau reach the nucleus and how AICD and Aβ control protein expression at the transcriptional level, (ii) post-translational modifications of AICD, Aβ, and Tau, and (iii) what these three molecules have in common.

Alzheimer disease (AD)2 is the most common form of dementia and a leading cause of death. Amyloid-β (Aβ) peptides of varying length (30–51 amino acid residues) are produced by the sequential, proteolytic processing of the amyloid precursor protein (APP) by β- and γ-secretases (1, 2). In the healthy brain, these protein fragments are normally degraded and eliminated. In the AD brain, the 42-amino acid peptide (Aβ42) is prone to form aggregated amyloid oligomers, which are believed to contribute to plaque formation and cognitive decline (3–6).

The γ-secretase also liberates an intracellular fragment called AICD composed of up to 50 residues depending on N-terminal variations (7–9). The first identification of the APP intracellular fragment (AICD) and its detection in brain tissue (8) immediately suggested that it has transcriptional activity, like the Notch intracellular domain (NICD). Whether amyloid Aβ represents a biologically inert bypass product of APP processing or can harbor its own function is a leading question in the AD field. Aβ is potentially toxic depending on its biophysical state (10). Equimolar amounts of the Aβ peptides and the C-terminal fragment AICD are derived from the β-C-terminal fragment C99 (11), which represents the APP fragment generated by the initial APP cleavage by β-secretase (Fig. 1).

A seminal discovery concerning the transcriptional regulatory function of the APP cytoplasmic tail was the observation of its complex formation with Fe65 and the histone acetyltransferase Tip60 and transcriptional activity in reporter gene assays (12). Transactivation of transcription requires γ-secretase activity and nuclear translocation of Fe65 but not of AICD under these assay conditions (13). However, other studies detected AICD in transcriptional complexes on promoters of target genes using ChIP (see below).

In addition, there is evidence that soluble APP fragments (sAPP) of the ectodomain can modulate gene transcription in stimulating downstream signaling through unknown sAPP receptor(s) (14). Accumulation of intracellular Aβ species in neuronal cells before plaque formation leading to concomitant loss of MAP2 expression suggested that Aβ may affect expression or turnover of other proteins (15–17). However, it was not clarified whether this occurs at the transcriptional or translational level.

Using a variety of techniques, the recently detected uptake of Aβ peptides into the nuclei of cultured cells (as well as in vivo) revealed that Aβ42 possesses unique modulatory activity (18). Direct evidence for the presence of (i) nuclear Aβ42 in wild-type animals, (ii) the increased level of nuclear Aβ42 in APP-overexpressing animals, and (iii) the detection of nuclear Aβ in quantities comparable with other transcription factors imply a certain biological relevance.

The second major hallmark of AD pathology is the presence of neurofibrillary tangles and is associated with intracellular Tau aggregates called neurofibrillary tangles and with modified Tau (19). Although the neuronal Tau (tubulin-associated unit) protein is mostly considered as an essential cytosolic factor for microtubule assembly, a similarly unexpected discovery was the nuclear localization of Tau in the early 1990s, first by the team of L. Binder, and confirmed later by many other groups, in neuronal as well as in non-neuronal cells (20–30). Until now, only a few studies have linked Tau to the regulation of gene expression. The involvement of Tau in the expression of calbindin, a calcium-binding protein, and of Baf-57, a protein of the chromatin remodeling SWI/SNF complex encoded by the SMARCE1 gene, was demonstrated in neuronal cultures (31, 32). A direct role for nuclear Tau in the transcription of these genes, however, has yet to be demonstrated.
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Possible Sources of Nuclear AICD, Aβ, and Tau

Out of 70 γ-secretase substrates, about 30 generate intracellular domains (ICD) with potential activity in transcriptional regulation (33), including AICD, which is mainly produced via the amyloidogenic pathway (34) and not released from plasma membrane-attached APP. The α-secretase-derived C-terminal stub C83 did not produce AICD (8). However, it is also conceivable that C83 derived from C99 by a secondary α-secretase cleavage could serve as a precursor of AICD. AICD generation could be blocked by β- and γ-secretase inhibitors (35, 36), which affected regulation of neprilysin expression (see below). Unlike the typical intramembranous γ-cleavage, AICD is released from e-cleavage sites located close to the cytosolic leaflet of the plasma membrane (9, 37). AICD is difficult to detect in cells and human tissues because it undergoes rapid inactivation by the mainly cytosolic and endosomal insulin-degrading enzyme, a metalloproteinase (38), and by caspases to yield a fragment called C31 (39). Insulin-degrading enzyme cleaves AICD at multiple sites, yielding numerous small peptides (40). There are studies describing the association of so-called adaptor proteins that function in the nucleus, nucleosome assembly protein SET and mediator (Med12), with AICD-Fe65 nuclear complexes (41, 42). Other factors increase Aβ production or lower AICD levels and were found to participate in the AICD-containing transcriptional protein complex, *e.g.*, Pat1, 14-3-3γ and CP2, the latter of which was suggested to mediate binding to the DNA (43).

Recent evidence suggests that the APP-like proteins 1 and 2 (APLP1, APLP2) are integral to Aβ and AICD generation. APLP1 and APLP2 share a conserved domain structure with APP but exhibit strikingly different localization with APP and APLP2 preferentially localized in intracellular vesicular structures, whereas APLP1 mainly localizes to the plasma membrane (44). The APP family proteins were reported to form homomeric and heteromeric complexes (45), and this complex formation may affect processing of the AICD domain. Formation of ICDs was also detectable for APLP1 (AL1ICD) and APLP2 (AL2ICD); however, AL1ICD and AL2ICD behave differently with respect to AFT (AICD-Fe65-Tip60)-like complex formation. Similar to AICD, AL2ICD together with Fe65 translocates into the nucleus and forms spherical nuclear AFT-like complexes, whereas nuclear complex formation was not detectable for AL1ICD. Moreover, APLP1 appears to affect AICD nuclear function in competing with APP for Fe65. In addition, the AL1ICD half-life is shorter depending on the N-terminal sequence generated during γ-secretase cleavage. This results form enhanced proteasomal degradation of AL1ICD and thus limits the nuclear signaling capabilities. APP and APLP2 also exhibit faster protein turnover than APLP1, which might be an explanation for why AL1ICD competes with APP (46, 47).

The main AICD species corresponds to AICD50–99 (CTF (C-terminal fragment of APP) residues 50–99), which is in agreement with the detection of Aβ49 (48) and its subsequent processing into Aβ40 (49). An alternative cleavage occurs and generates AICD49–99, which is N-terminally extended by one amino acid that begins at Leu-49 according to Aβ numbering, which is in agreement with the detection of Aβ48 and molecules of the Aβ42 peptide series (49, 50). Overall, it is clear that e-cleavage is a limiting step for the subsequent γ-secretase γ-cuts. Oestereich *et al.* (51) have shown that AICD 50–99 (VMLKKK . . .) is rather stable as compared with AICD49–99 (LVMLKKK . . .), which starts with a destabilizing residue (Leu), when the mutant T43V enhances dimerization of APP (Fig. 2).

Depending on the alternative splicing of exons 2, 3, and 10, six isoforms of Tau are expressed in the adult human brain containing 0 (0N), 1 (1N), or 2 (2N) inserts in the N-terminal part of Tau, and 3 (3R) or 4 (4R) microtubule-binding domains (MTBDs). Profiling murine brains with isoform-specific Tau antibodies revealed the predominant localization of Tau 1N in the soluble nuclear fraction, as compared with the 0N and 2N isoforms (23). Phosphorylation is the most studied post-translational modification associated with the nuclear form of Tau. In neuronal or non-neuronal cells, nuclear Tau has been widely detected using pan-Tau antibodies. Further studies using various antibodies directed against phospho-dependent Tau epitopes confirmed the predominantly hypophosphorylated form of Tau in cell nuclei (20, 24, 27, 29, 52). Using the Tau1 antibody directed against a non-phosphorylated epitope of Tau protein (serine 195–202), differences in the sub-nuclear localization of Tau have been observed between human and murine cells. In human brain and interphase non-neuronal cells, the
Tau1 antibody detects a unique nucleolar localization of Tau (24, 26, 28), whereas a diffuse Tau1 labeling is observed in murine neuronal cells (27).

Changes in the phosphorylation states of Tau can occur during oxidative and/or hyperthermic (a strong oxidative stress inducer) conditions. Such stresses trigger the dephosphorylation of cytoplasmic Tau, which is correlated with its nuclear accumulation. After recovery from stress, the amount of nuclear Tau returns to basal levels, whereas the phosphorylated level of cytoplasmic Tau increases over basal levels. These findings suggest that phosphorylation/dephosphorylation represents a major mechanism to regulate the nucleo-cytoplasmic shuttling of Tau. Using PHF-1 monoclonal antibody (recognizing phospho-serines 396 and 404), phosphorylated forms of Tau have been detected in the nuclei of neurons under pathological conditions, e.g. in human brain from presenile dementia with motor neuron disease (54), as well as in neuroblastoma cells treated with formaldehyde (55) or infected with herpes simplex virus type 1 (56). PHF-1 labeling had also been detected in the nuclei of the neuritogenic rat brain cell line B103 (22). The nucleo-cytoplasmic shuttling of Tau may also be mediated by O-GlcNAc glycosylation, which has been correlated with reduced nuclear Tau localization in human non-neuronal cells (57).

**AICD, Aβ42, and Tau Interactions with DNA**

Although the past decade of research has established the role of AICD as a factor with transcriptional regulatory function, the net effect of AICD on gene expression is still controversial (for a summary, see Ref. 43). Several studies have confirmed the presence of AICD in the nucleus where it is associated together with Fe65 and Tip60 (8, 58, 59). In other studies to identify AICD-regulated genes, however, the binding of AICD to regulatory cis-elements has only been demonstrated for a limited set of genes. The targets that have been reported to be up-regulated included the metastasis suppressor KAI1/CD82 (60, 61), the tumor suppressor TP53 (62), the Aβ-degrading enzyme neprilysin (NEP) (42, 62–64), the endoplasmic reticulum stress and unfolded protein response gene CHOP/DDIT3 (C/EBP homologous protein/ DNA damage-inducible transcript 3) (65), and sonic hedgehog receptor Patched (PTCH1) (66). In contrast, down-regulated targets included the epidermal growth factor receptor (EGFR) (67) and the low density lipoprotein receptor-related protein 1 (LRP1) (68). Although not formally defined as direct targets, the glycogen synthase kinase3β (GSK3β) (59, 69, 70), APP (59) itself, and BACE1 (59) are considered AICD-regulated genes. However, it has to be noted that other studies did not observe a nuclear transcriptional role of AICD at least with respect to the expression of some of the potential target genes (71–73).

Among the currently known interaction partners, the adaptor protein Fe65 is of special interest with respect to the AICD nuclear function. Fe65 binds to the C-terminal domain of APP in a phosphorylation-dependent manner, and after γ-secretase cleavage, the AICD-Fe65 complex translocates to the nucleus (59). Together with the Tip60 histone acetyl transferase, AICD then forms a trimeric spherical nuclear AFT complex that exhibits transcriptional activity. Although transgenic mice expressing AICD and Fe65 exhibit pathological features of AD (74), the precise molecular mechanism remains unresolved (i.e. does the central YENPTY motif of nuclear AICD directly interact with the phosphotyrosine-binding domain 2 (PBT2) of Fe65 (60); see review in Ref. 33). At present, the generally accepted view is that AICD could function as a transcription factor in the AFT complex.

Similarly to AICD, Aβ42 has also been found to associate with regulatory elements of KAI1 and LRP1 within 30 min (after application) in ChIP experiments (18). Interestingly, Fe65 and histone acetyl transferase Tip60 were only detectable after 60 min, indicating that Aβ42 translocated to the nucleus independent of Fe65 in contrast to AICD (59). Association of Aβ42 with the KAI1 promoter induced the release of the repressor NCoR, which was previously reported as a prerequisite for association of Tip60 during studies of the regulation of KAI1 expression (61, 75, 76).

Many years before the first description of nuclear Tau localization, Avila and co-workers (77–79) demonstrated the capacity of microtubule-associated proteins (MAP), including Tau, to bind DNA. Several in vitro studies have since confirmed the capacity of Tau to bind DNA and to induce its conformational change (26, 80–84). The presence of endogenous Tau-DNA complexes has been described in primary neuronal cultures and, under hyperthermic stress conditions, increased Tau lev-
els in neuronal nuclei have been correlated with an increase of Tau-DNA complex formation (27). Whether Tau binds directly or not to neuronal DNA has yet to be demonstrated.

*In vitro*, Tau displays similar affinities for DNA and microtubules (84), and both of these Tau-mediated interactions are reversible (82, 84). Tau has been reported to bind single- and double-stranded DNA via the minor groove (26, 27, 84, 85), thereby drawing parallels between Tau and histones in terms of DNA binding. Indeed, monomers or small oligomers of Tau can bind to DNA complexes and give rise to a “beads-on-a-string” organization like histone-DNA assembly (80, 84), thus suggesting that Tau could act like a chaperone (26, 27, 84). Although larger aggregates of Tau interact only weakly with DNA (84, 86), complexes between large Tau aggregates and DNA have been observed *in vitro*, suggesting that different Tau-DNA structures exist (84). Tau phosphorylation has also been shown to prevent its binding to DNA (84, 86, 87) and reported to alter DNA folding (53). Moreover, Hua and co-workers (99) described that Tau protected DNA from thermal denaturation (while improving its renaturation), whereas Padmaraju et al. (81) showed that Tau may nick the supercoiled DNA.

Although Tau does not display any specificity toward a particular DNA sequence (78, 84), EMSAs have proven that the proline-rich domain of Tau is important for mediating its interactions with DNA (80). More recently, NMR studies have further demonstrated that the Tau amino acids involved in its interaction with oligonucleotides containing a murine pericentromeric satellite DNA sequence (87) are mainly localized to the second half of the proline-rich domain (PRD) of Tau and the R2 repeat present in the microtubule-binding domain. In human non-neuronal cells, the nucleolar localization of Tau appears to be mediated by AT-rich DNA sequences organized as constitutive heterochromatin. In neuronal cultures, results obtained with netropsin, which is a polyamide with antibiotic and antiviral activity, suggested that *in situ*, Tau may also interact with DNA through the AT-rich minor groove (27).

**Possible Nuclear Functions of AICD, Aβ, and Tau**

Fe65 and the histone acetyl transferase Tip60 and AICD form a tripartite complex (12) and AICD increased Fe65-mediated nuclear signaling, but the two proteins did not traffic together to the nucleus (88). Still, it has to be investigated how different transcriptional co-factors associated with AICD-containing transcription complexes may induce context-specific changes in gene expression patterns.

Regarding Aβ42, it appears that low-n oligomers (from dimers to octamers) of Aβ42 peptides in the nucleus induce changes in gene transcription (18). At present, it is not clear whether Aβ42 is binding to the KAI1 or LRP1 promoters or whether binding to DNA may affect DNA or chromatin structure (89). At the RNA level, Aβ42 treatment of SH-SY5Y cells induced a down-regulation of KAI1 and LRP1 expression within the first 6 h, whereas APP mRNA levels were up-regulated between 6 and 8 h after the addition of Aβ42. These effects were specific for Aβ42 and not detectable with peptides Aβ43 and Aβ38 or Aβ42G33A, which is a substitution peptide known to form oligomeric β-pleated sheet complexes more readily than Aβ42 WT peptide (90). Moreover, Aβ42 had no effect on the expression of the Notch target HES1 (18). Although LRP1 and APP are similarly regulated as by AICD, KAI1 is down-regulated by Aβ42 and up-regulated by AICD. This finding suggests a different mechanism of transcriptional modulation by Aβ42 and AICD. A recent microarray analysis identified 225 genes that are differentially regulated in response to Aβ42 treatment including IGFBP3 and IGFBP5, as well as ID1–3 and LMO4 (91).

It has been demonstrated that nuclear Tau plays a key role in DNA protection under stress conditions (27). *In vitro*, Wei et al. (80) showed that Tau-DNA binding protected DNA from damage induced by free hydroxyl radicals, likely through its capacity to bind to the AT-rich minor groove of DNA (*i.e.* a common way for proteins to physically protect DNA from damage by inducing its bending). Going a step further, in primary neuronal cultures, endogenous hypophosphorylated nuclear Tau was shown to protect DNA integrity under oxidative and hyperthermic stress conditions (27). The DNA protective function of Tau has been validated *in vivo* in adult neurons in the brain of mouse submitted to hyperthermic stress and under physiological condition (29). Although Tau may protect DNA integrity through AT-rich minor groove binding (27), it does not preclude the involvement of Tau in the DNA damage response (29).

DNA damage is highly deleterious in neurons and may trigger transcriptional dysregulation as observed in AD brain (92, 93). Tau hyperphosphorylation in nuclei correlated with DNA alteration in neuroblastoma cells after formaldehyde treatment. In an *in vivo* mouse model of Tau pathology (THY-Tau22), hyperphosphorylation and formation of prefibrillar Tau oligomers in the nuclei of hippocampal neurons correlated with accumulation of DNA damage (oxidation and strand breaks), suggesting that Tau phosphorylation and oligomerization may alter the DNA protective function of Tau and be involved in the accumulation of oxidative DNA damage observed in AD brain at early stages of the disease.3

**The Interplay between AICD, Aβ, and Tau**

By deciphering the mechanisms by which AICD and Aβ are generated and how their production is regulated, our understanding of how AICD, Aβ, and Tau are involved in the pathophysiology of AD will advance. Although their potential roles in regulating gene expression are currently not well understood, significant progress is being made. For example, we have shown that the nuclear accumulation of Aβ peptides, other than Aβ42, is independent from the recruitment on gene promoters (18). We found that Aβ42 and Aβ42G33A accumulate equally well in the nucleus, but only Aβ42 can actively regulate gene expression. When we compared possible overlapping targets of AICD and Aβ, we found that both repressed LRP1 and up-regulated APP. In this context, it has to be mentioned that another study did not see an effect of Aβ42 on LRP1 expression (68). Moreover, although AICD increased the transcription of KAI1 (CD82), Aβ42 was also associated with the KAI1 promoter in

3 M. Violet, A. Chauderlier, L. Delattre, M. Tardivel, M. Sendid Chouala, E. Marciniak, S. Humez, L. Binder, R. Kayed, B. Lefebvre, E. Bonnefoy, L. Buée, and M. C. Galas, in revision.
ChIP experiments but down-regulated KAI1 expression at the mRNA level. It is still unclear whether Aβ42 in directly binding to DNA modulates gene expression by affecting DNA helicity (94) and chromatin structure or whether it acts in association with specific DNA-binding factors similar to AICD.

An enzymatic impairment of APP proteolysis by the inhibition of the γ-secretase (which means an inhibition of AICD and Aβ generation) using several cell lines resulted in divergent outcomes regarding the protein or mRNA levels of the putative AICD-regulated genes (42, 63, 71) including neprilysin (NEP/MME) (95). Based on the finding that AICD itself was shown to stimulate the activity of the gene promoter of the Aβ-degrading enzyme NEP, which increased the level of this protein in HEK293 cells (33) and led to enhanced degradation of Aβ monomers, it is technically challenging to differentiate between the effects caused either by AICD or by Aβ. Moreover, AICD and Aβ42 increased the transcription of its own precursor gene APP (Fig. 3).

The exact mechanism of how Aβ affects gene regulation needs further explorations, e.g., by an investigation of the role of co-factors that are involved, i.e., Fe65 and Tip60. Nuclear Fe65 may even play a key role in the response of the cell to DNA damage similar to Tau. Transgenic mice co-expressing both AICD and Fe65 show increased transcription of GSK3β that was accompanied by phosphorylation of Tau (74), which could mean that AICD may modulate the DNA binding capacity and the DNA protective function of Tau.

NEP is central for the understanding of APP-mediated gene regulatory activities because it seems to be regulated by AICD. An AICD-mediated increase of NEP could alter the ratio of Aβ42/Aβ40 because NEP was shown to degrade the latter peptide more efficiently (only Aβ42 regulates gene expression), which creates another level of complexity. Changes in the ratio of Aβ42/Aβ40 in turn may easily lead to the exacerbation of cellular amyloid toxicity.

**Conclusion**

Over the past 30 years, Tau and APP metabolites have been investigated as toxic aggregates in the pathogenesis of AD. More recent studies suggest that these end-stage hallmarks of the disease may be prompted by earlier, subtle changes such as the dysregulation of nuclear gene expression. Strict control over the nuclear levels of AICD, Aβ, and Tau may be critical to prevent the dysregulation of neurodegeneration-associated genes. However, for most of these target genes, direct association of AICD, Aβ, or Tau with transcription complexes and
regulatory effects on their transcription has to be proven. The present review illuminates new insights about AD etiopathogenesis and underscores the need for added research to advance our understanding of the effect of AICD, Aβ, and Tau on the nucleus.

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