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Review

The amyloid precursor protein: A biochemical enigma in brain development, function and disease

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ABSTRACT

For 20 years the amyloid cascade hypothesis of Alzheimer disease (AD) has placed the amyloid-β peptide (Aβ), formed from the amyloid precursor protein (APP), centre stage in the process of neurodegeneration. However, no new therapeutic agents have reached the clinic through exploitation of the hypothesis. The APP metabolites, including Aβ, generated by its proteolytic processing, have distinct physiological functions. In particular, the cleaved intracellular domain of APP (AICD) regulates expression of several genes, including APP itself, the β-secretase BACE-1 and the Aβ-degrading enzyme, neprilysin and this transcriptional regulation involves direct promoter binding of AICD. Of the three major splice isoforms of APP (APP_{695}, APP_{751}, APP_{770}), APP_{695} is the predominant neuronal form, from which Aβ and transcriptionally-active AICD are preferentially generated by selective processing through the amyloidogenic pathway. Despite intensive research, the normal functions of the APP isoforms remain an enigma. APP plays an important role in brain development, memory and synaptic plasticity and secreted forms of APP are neuroprotective. A fuller understanding of the physiological and pathological actions of APP and its metabolic and gene regulatory network could provide new therapeutic opportunities in neurodegeneration, including AD.

1. Introduction

Alzheimer's disease (AD) and related dementias constitute a spectrum of age-related neurodegenerative diseases leading to major cognitive and behavioural deficits. AD is a global problem affecting over 30 million people worldwide and some 10 million in Europe alone with lesser developed countries predicted to harbour 70% of dementia cases over coming decades, creating a rapidly growing epidemic. It is now just over 20 years since the amyloid cascade hypothesis was formulated to provide a framework for explaining the biochemical mechanisms underlying the neurodegenerative processes occurring in Alzheimer's disease and for the design of potential therapeutics [1]. The hypothesis places the 40–42 amino acid, amyloid β-peptide (Aβ), derived by proteolytic processing of the membrane glycoprotein amyloid precursor protein (APP), centre stage in the cell death process. Recent reappraisals of the hypothesis have, however, highlighted that Aβ-independent factors may also contribute to the disease process and that oligomeric forms of Aβ may be the principal toxic agents [2–4]. Furthermore, no new therapeutic agents have reached the clinic based on exploitation of the amyloid cascade hypothesis [5]. A variety of factors probably contribute to this, especially the limitations in the animal models currently available, which are based on the rare, familial forms of the disease, and the heterogeneity of the late-onset forms of AD. We, and others, have hence emphasised that a major unmet scientific need in the AD field is to understand completely the normal biochemistry of APP, and the physiological roles of its key metabolites, in order to clarify what is happening in the disease situation. Indeed, APP is more than just an "amyloid precursor" but is expressed ubiquitously as a type I membrane glycoprotein and has specific biochemical and pathological roles in other tissues which are generally ignored since its historic origins unsurprisingly led to a predominant focus on AD-related mechanisms. For example, APP is a primary androgen target gene that promotes prostate cancer growth and which is up-regulated also in colon and pancreatic tumours implying a general role for the protein in cell growth, differentiation and carcinogenesis [6,7].

2. APP isoforms and metabolism

APP is expressed in both neuronal cells and extra-neuronal tissues [8] and belongs to a larger evolutionarily conserved APP superfamily found in diverse organisms from nematode to man

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[9] which, in mammals, consists of APP itself and APP-like proteins APLP1 and APLP2 (Fig. 1). In *Drosophila melanogaster* and *C. elegans* their APP homologues have been named APPL and APL-1, respectively [10,11]. In, neuronal cells, it is anterogradely transported in vesicles by kinesin-mediated fast transport to various cell compartments including synapses [12], reviewed in [13]. There are three major isoforms of APP (APP_{695}, APP_{751}, APP_{770}) generated as a result of alternative splicing of exons 7 and 8. Compared with APP_{695}, the APP_{751} isoform contains an additional Kunitz-type protease inhibitor (KPI) domain and the 770 isoform also contains a 19-amino acid, OX-2 domain. APLP2 more closely resembles APP_{770} in domain composition whereas APLP1 is more similar to APP_{695} (Fig. 1). In brain, APP_{695} is principally neuronal and is expressed at relatively high levels compared with the other two isoforms. In human cortex the ratio of different APP isoform mRNAs is approx $APP_{770}/APP_{751}/APP_{695}$ = 1:10:20, although there are regional differences. In AD brain the various isoforms show different temporal- and disease-specific expression implying they exert distinct functional and metabolic roles [14,15]. Until recently, no clearcut functional differences have been ascribed to the different APP isoforms apart from the protease-inhibitory role of the KPI domain. However, it appears that the neuronal APP_{695} isoform is preferentially involved in regulation of gene expression [16], as detailed in Section 6.

APP isoforms were shown to be differentially expressed during brain maturation [17] and alternative splicing and processing of the APP gene was found to be regulated by various factors, including hormones, growth factors, phorbol esters and interleukins [18–20]. The regulatory region of the APP gene contains consensus sites recognised by the transcription factor, specificity protein 1 (SP1) [21]. Recently microRNAs, which represent small, non-coding RNAs interacting with target mRNA and mediating translational inhibition or transcript destabilisation, were suggested to regulate APP gene expression and to play an important role in neurodegeneration [22]. In particular miR-101 and miR-153 were shown to down-regulate expression of APP in human cell cultures suggesting their relevance to AD pathology [23,24].

APP is expressed in various organs and tissues. Northern blot analysis has demonstrated that, in rat, endogenous APP mRNA is expressed significantly more in the brain, kidney and lung compared to heart and liver. A similar APP expression pattern was also seen when the human APP transgene, driven by the ubiquitin-C promoter, was introduced to the animals aiming at producing a rat model of AD. The tissue specificity of APP expression suggests the presence of regulatory elements within the cDNA sequence of APP determining the character of its expression [25]. However,

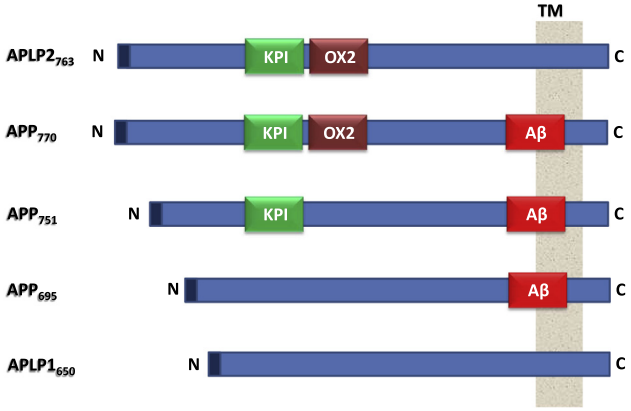

Fig. 1. Schematic representation of the proteins from the APP family and their main domains. They are all type I transmembrane glycoproteins. APLP1 and APP_{695} both lack the KPI and OX2 domains, contained in APLP2 and APP_{770} while APP_{751} has only the KPI domain.

there are some data suggesting that membrane localisation and processing of APP in neurones differ from those in peripheral cells (e.g., lymphoid cells, hepatocytes or kidney) which suggests that functioning of this transmembrane holoprotein and production of Aβ in the brain is a critical determinant of its receptor-transducer properties unique to this organ [26]. Abnormal APP metabolism in the pancreas is also linked to the pathogenesis of type 2 diabetes and strong epidemiological evidence suggest a link between diabetes and AD [27] and AD has been referred to as type 3 diabetes [28].

Despite APP from various species being characterised by a rather significant conservative amino acid sequence, rodent APP in the region of Aβ peptide differs from human by 3 amino acids (Arg^5 is substituted by Gly, Tyr^{10} by Phe and His^{13} by Arg) which makes rodent Aβ less prone to form amyloid aggregates [29]. As recently suggested, His^{13} in Aβ peptide is critical for the ability of the peptide to bind Zn which is required for initiation of fibrillogenesis [30]. Because of this difference in the Aβ peptide structure, rodent models of AD require the over-expression of human APP and/or other proteins involved in human AD pathology, which brings some limitations to the utilisation of mouse and rat models of AD for a full understanding of the pathology of this human disease. Furthermore, there is also a proteolytic processing difference between species, as the sequence differences in mouse versus human APP also protect against β-secretase processing [31].

Platelet and leukocyte APP isoforms are processed using mechanisms similar to those in neuronal cells to generate Aβ and soluble forms of APP [32]. They therefore potentially provide a peripheral model of APP biochemistry and perhaps a mirror into abnormalities in APP processing in the brain. In the transition from normal to mild cognitive impairment to AD, a small but significant shift in the ratio of platelet APP isoforms from the larger to the smaller forms has been consistently observed [33–35] and has been suggested as a possible AD biomarker. However, when utilising extra-neuronal cells as models for studying APP metabolism and its effects, interpretation of data may be influenced by the nature of the isoforms endogenously expressed in these cells.

3. APP processing

There are two divergent pathways of APP metabolism occurring naturally (Fig. 2), of which the minor (amyloidogenic) pathway involves the consecutive actions of two membrane-bound aspartic proteinases generically termed β- and γ-secretases [36,37]. This pathway generates not only Aβ but a number of other physiologically active metabolites, including the cleaved intracellular domain (AICD), which could all contribute to, or ameliorate, the pathological processes leading to AD. More than 90% of APP metabolism, however, normally involves the initial alternative cleavage of APP by a zinc metalloproteinase termed α-secretase followed again by γ-secretase. Since α-secretase cleaves APP within the Aβ peptide region, it prevents Aβ formation and activation of this pathway is hence potentially neuroprotective. Some recent data suggest that subcellular trafficking of APP to the non-amyloidogenic pathway is regulated by huntingtin associated protein-1 (HAP-1) since down-regulation of the latter in neurons results in increased production and accumulation of Aβ [38].

The γ-secretase mediated cleavage of APP C-terminal membrane-bound fragments formed after α- or β-secretase action on the holoprotein is but one example of the general phenomenon of intramembrane proteolysis [39,40] and is analogous to the cleavage of the Notch receptor in the Notch signalling pathway. The γ-secretase complex with its catalytic presenilin (PS) core functions as a promiscuous aspartic protease able to act on a diverse range of membrane protein substrates and showing flexibility in its site of cleavage of susceptible substrates. These

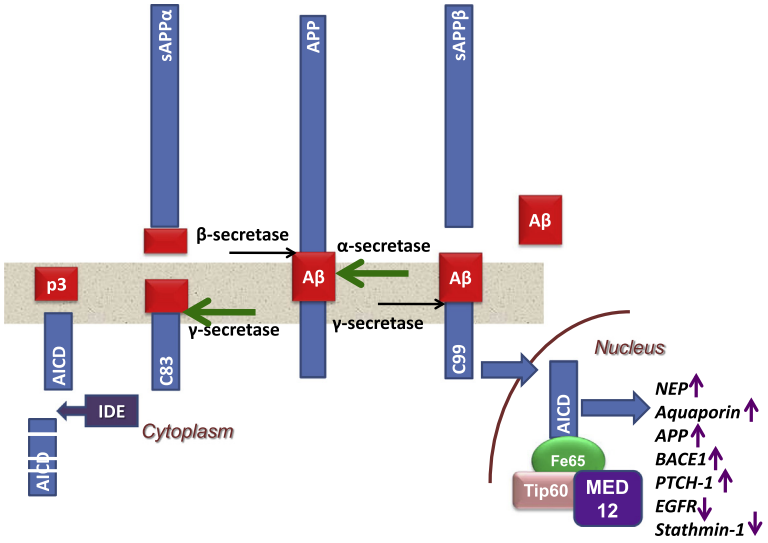

Fig. 2. Proteolytic processing of APP and generation of functionally active AICD. The β-,γ-secretase amyloidogenic pathway principally mediates the nuclear signalling by AICD. Some of the genes reported to be regulated by AICD are indicated. For a more complete listing, see [37,80]. sAPPα, soluble form of APP produced by α-secretase cleavage; sAPPβ, soluble form of APP produced by β-secretase cleavage.

proteolytic pathways and their aberrant actions in AD are fully described in this issue [41] and here we will focus on the APP isoforms and the generation of the intracellular domain of APP (AICD) and its physiological and pathological actions, particularly in signalling from membrane to nucleus through epigenetic modulation of gene expression.

4. APP and normal brain functions

Although still not fully understood, the role of APP in normal functioning of the brain and other organs had been intensively studied. The protein sequence analysis of the APP superfamily members strongly suggests that the normal function of APP relates to cell–cell interaction and cell–substrate adhesion [11,42] consistent with a role in development. Several recent studies confirmed that, in developing brain, APP is required for neuronal precursor cells to migrate correctly in the nascent cortical plate [43] and that this effect of APP requires its interaction with products of other proteins, DISC-1, and Disabled-1 [44]. The most recent data also suggest that pancortins, proteins expressed in developing and mature brain cortex and reducing the activity of β-secretase, interact with APP promoting neuronal cell migration [45]. APP was also shown to play an important role in cell cycle progression of neural stem cells, through the interaction of APP with amyloid precursor protein binding protein-1 (APP-BP1). In rat, substantial expression of both APP-BP1 and APP was observed in embryonic brain and in the early postnatal period (up to P12) with only low levels of APP-BP1 found in the adult brain [46]. During embryogenesis the APP_{695} isoform was shown to be the major form involved in embryonic brain maturation [47]. Apart from brain development, APP is also required for formation of neuromuscular junctions where APP co-localises with acetylcholine receptors [48].

APP has many other interacting proteins and the APP interactome may play important roles in regulating its trafficking, processing and signaling effects [49]. The increase of APP levels during synaptogenesis suggests a functional role of this protein in the process of neuronal network formation. Confocal microscopic analyses in primary neurons showed colocalization of APP with synaptic vesicle proteins among which synaptotagmin-1, a resident synaptic vesicle protein, directly binds to APP. This allowed the authors to suggest that APP interacts with the calcium sensor of synaptic vesicles and as such might play a role in the regulation of synaptic vesicle exocytosis [50].

One of the important neuronal functions recently described for APP is to maintain neuronal calcium homeostasis and cell oscillations which is essential for synaptic transmission and neuronal networking [51]. This was based on the observation that APP over-expression inhibits spontaneous synchronous calcium oscillations in rat cortical neurones in culture and that phosphorylation of T668 in the APP intracellular domain is needed for this effect [52]. The role of APP in learning and memory is substantiated by studies showing that regulation of its level of expression can modulate synaptic spine density, which is mediated predominantly via its soluble, α-cleaved APP ectodomain (sAPPα) [53,54]. Furthermore, both APP and APLP2 are essential at PNS and CNS synapses for spatial learning and long-term potentiation (LTP) [55].

In adult brain APP has been also suggested to play an important role in axonal outgrowth and restoration of neuronal functions after injury. Thus, in the *Drosophila* head injury model, APP was shown to be up-regulated up to 7 days after the impact [56] and this observation was confirmed in APP overexpressing mice which had more efficient sciatic nerve regeneration after injury due to better organisation of regenerating fibres. In these mice, APP was also shown to prevent neuropathic pain [57].

Among numerous physiological functions ascribed to APP, one is related to its ferroxidase and iron-trafficking properties suggesting that some neurotrophic properties of APP and its fragments could be mediated by iron regulation [58]. On the other hand, iron regulates APP mRNA expression suggesting a role for iron in the metabolism of APP [59]. Similarly, it was shown that copper can regulate APP expression and supporting a hypothesis on a role for APP in copper homeostasis. Both iron and copper-regulated APP expression were suggested as potential therapeutic targets in AD [60].

Reconstitution experiments with APP_{695} suggested that APP can act as a receptor-like protein that could operate through a G protein [61] and regulation of G_o GTPase activity by APP was confirmed by Brouillet and colleagues [62]. More recent work suggested that neurotoxicity of Aβ is mediated by a mechanism that involves APP-dependent Go protein activation and that a

receptor-like function of APP might be implicated in neuronal degeneration in AD [63]. In neuronal cells APP was found to localize not only in the plasma membrane but also in mitochondria where it can enter, interacting with the import receptors [64]. Accumulation of APP and Aβ observed in mitochondria of AD mice and patients results in mitochondrial dysfunction and impairment of cell energy metabolism in the brain [65,66].

5. APP and cellular response to hypoxia and ischaemia

APP metabolism was shown to undergo significant changes during ageing and in response to various environmental factors which is considered to be one of the mechanisms contributing to the development of sporadic forms of AD [67]. There are data demonstrating that amyloid metabolism is affected by ischaemia and hypoxia and that an increased level of APP is a part of the acute adaptive response of the brain to hypoxia [68]. Levels of membrane bound APP were found to be significantly increased in rat neocortex after severe hypoxia. However, this effect was less pronounced in the group of animals subjected to hypoxic preconditioning prior to severe hypoxia [69]. The analysis of the protein levels of soluble and membrane-bound forms of APP in the neocortex and hippocampus of rats subjected to severe hypoxia and severe hypoxia with preconditioning has demonstrated that an increased ADAM17 expression in preconditioned animals 24 h after hypoxia corresponded to higher levels of the soluble form of APP and a reduction of the membrane bound fraction which confirmed a role for ADAM17 in APP shedding [69]. According to our own data prenatal hypoxia also resulted in increased levels of APP in the brain of rats during postnatal development. Moreover, levels of APP in rat cortex and hippocampus also increased after ischaemia caused by four-vessel occlusion [70]. Recently, using *APP*$^{-/-}$ and *BACE*$^{-/-}$ mice, it was demonstrated that APP regulates cerebral blood flow in response to hypoxia, and that its cleaved fragments are crucial for rapid adaptation to ischaemic conditions [71].

Although up-regulation of APP levels is considered neuroprotective in hypoxia and ischaemia, it can also lead to an increased production of Aβ due to activation of BACE1 and reduced levels of the amyloid-degrading enzymes neprilysin (NEP) and endothelin converting enzyme-1 (ECE-1) [70,72]. Reduced levels of NEP expression caused by hypoxia were recently linked to histone modifications in the *NEP* gene promoter [73]. The decrease of *NEP* expression in NB7 neuronal cells caused by hypoxia [74] is linked to activation of caspases and reduced binding of AICD to the *NEP* promoter [75]. Intriguingly, PS1/2 mutations identified in Alzheimer patients differentially affected the hypoxic response, involving the generation of AICD. Together, these results suggest a direct role for PS in the regulation of the oxygen sensing pathway via the APP/AICD cleavage cascade [76].

Other types of stress (e.g., restraint stress) were also demonstrated to affect APP expression differentially affecting levels of the neuronal APP_{695} isoform, particularly, in the amygdala of rats. Up-regulation of APP_{695} levels in the amygdala after restraint stress is considered to participate in the brain stress response maintained by the basolateral amygdaloid nucleus [77].

6. APP and gene regulation

The prediction and first report of a γ-secretase cleaved C-terminal intracellular domain of APP (originally named AID) was provided by [78] who identified its presence in brain tissue from normal subjects and AD patients and showed that this fragment could induce apoptosis. Hence, this led to the suggestion that the toxic effects of APP processing may not just be due to Aβ alone. Following from this, Cao and Sudhof [79] were able to show that the C-terminal domain (now generally termed AICD) could form a complex with the nuclear adaptor protein Fe65 and the histone acetyltransferase Tip60, which could stimulate gene transcription in a heterologous reporter system but they did not identify any endogenously regulated genes. Since that time numerous studies have produced a profusion of data both supporting and refuting a significant impact of AICD on transcriptional activity [80,81]. A possible explanation for the failure to detect changes in previously reported genes is that these genes are not affected by lack of APP under resting conditions or only in a small subset of cells and that AICD normally has a relatively minor effect on basal gene expression. Furthermore the nature of the particular model systems used (cell types, constructs used, cell density and ageing, transgenic animal models, etc.) may significantly affect results creating difficulties in comparing between apparently conflicting studies (discussed in [40,82,83]).

An additional complexity is that γ-secretase shows flexibility in its site of C-terminal cleavage of APP, and AICD is generated by prior cleavage of APP at the so-called ε-site following initial release of its ectodomain [84,85]. It has been speculated that familial AD mutations in presenilin may affect ε-cleavage, not only of APP but also of the many other γ-secretase substrates (e.g., cadherins), leading to changes in levels of the intracellular domains with signalling properties and increased levels of the membrane-bound fragments which can themselves be cell toxic. Such mechanisms may contribute to the toxicities associated with clinical trials using γ-secretase inhibitors [86,87]. Other studies have suggested that FAD mutations have a very variable effect at the ε-cleavage site, and that the main effect of the mutations is on the intermediary Aβ generating steps, e.g., [88].

Although all three APP isoforms are potentially amyloidogenic, it has now been shown that, in neuronal cell lines, sAPPβ, Aβ and AICD are preferentially formed from the neuronal APP_{695} isoform [16]. This observation supports a previous report that, in humans, Aβ is specifically formed in vivo from the APP_{695} isoform since the KPI-containing isoforms were preferentially cleaved by the α-secretase [89]. In addition only APP_{695}, when expressed in neuronal cell lines, increased nuclear AICD levels and *NEP* expression [16]. We have hence emphasised that it is nuclear, rather than total cellular, AICD levels that reflect AICD functional in gene regulation [16]. The APP isoforms themselves can exist in homodimeric forms with the KPI and transmembrane regions being involved in dimerization, which causes APP_{751} to be more efficiently processed through the non-amyloidogenic pathway than APP_{695} an event occurring at the cell-surface, probably by selective regulation of APP trafficking [90,91]. Wild-type APP_{695} is preferentially trafficked through the amyloidogenic endosomal pathway where it co-localises with BACE-1 promoting β-cleavage and subsequent formation of Aβ and AICD. This is a cholesterol- and lipid raft-mediated process [16,92,93].

Examples of genes that have been linked with AICD regulation include genes directly linked to AD: *APP* itself, *BACE-1*, and *NEP* (Fig. 2), the latter Aβ-degrading enzyme having contributed to a greater understanding of the underlying molecular mechanisms involved [94,95]. Relatively little is known of the nuclear complexes involving AICD and their functional significance. A number of earlier studies had convincingly demonstrated that AICD could associate with Fe65 protein and the histone acetyltransferase Tip60 to form a stable transcriptional complex. Until very recently, however, other components that may contribute to this process had not been identified. Two studies have now, however, significantly advanced our molecular understanding of AICD interactions in gene transcription. In the first of these, by screening for proteins that interact with the C-terminal tail of APP or its homologues, were able to identify a key interacting protein as a component of the key eukaryotic transcriptional mediator complex, namely

MED12 [96,97]. This hence provided a link to the transcription machinery validating the regulatory mechanism acting through AICD (Fig. 2). In brief, AICD can recruit the mediator complex to AICD-binding promoter regions depending on the presence of MED12. This study not only validated some of the previously identified genes responsive to AICD e.g., *NEP* and *aquaporin-1*, but also a number of other genes [98]. Based on these results, a map of the AICD-associated nuclear interactome was depicted [99]. Specifically, AICD can activate CUX1 transcriptional activity, which may be associated with AICD-dependent neuronal cell death. This work helps to understand the AICD-associated biological events in AD progression and provides novel insights into the development of AD. Our current hypothesis is that one of the physiological roles of APP is modulation of the epigenome supported by the recent report that over-expression of APP containing the Swedish mutation predisposing to AD switches global gene expression towards AD pathogenesis [100].

The cytoplasmic tail of APP has more than 20 interacting protein partners which connect APP to different intracellular signalling pathways including regulation of transcription, apoptosis and cytoskeletal dynamics. These partners include members of the Fe65, X11 and MINT families of proteins and in this way the AICD domain can control localization of membrane associated proteins in turn affecting the cellular transcriptome [101]. The mechanisms involved in these regulatory processes underlying AICD action have been summarized in [40,83].

The remodelling of chromatin provides the major regulatory mechanism for regulating gene expression. Such epigenetic mechanisms may contribute to the various risk factors (ischaemia, hypoxia, oxidative stress) and pathological events that predispose to sporadic AD (Fig. 3). The effect of familial mutations on the cellular transcriptome may be mediated in part through direct AICD activity or alternatively through an indirect response to Aβ accumulation. Chromatin remodelling, involving enhanced histone acetylation, is associated with the increased expression of several genes important for learning and memory [102]. On the contrary, transcriptional repression by histone deacetylases (HDACs) has been linked to memory impairment in aged animals [103]. Following our cellular based studies in which we demonstrated that HDAC inhibitors can upregulate expression of *NEP* through cdisplacement of HDAC1 by AICD [95], we have recently shown that the general HDAC inhibitor and anti-convulsant, sodium valproate, can attenuate memory deficits and up-regulate *NEP* activity in an adult rat model [70]. Since several distinct HDACs are involved in chromatin regulation, more selective HDAC inhibitors may represent better tools for targeted gene regulation and provide a novel therapeutic avenue for treatment of neurodegenerative diseases, including AD. In this context, HDACs 1 and 3 are of particular therapeutic interest in relation to neurodegeneration and cognition [104].

Given the potential involvement of APP in carcinogenesis, it is noteworthy that treating pancreatic and colon cancer cells with the HDAC inhibitors sodium valproate or trichostatin A led to down-regulation of APP. This in turn was mediated by prior up-regulation of GRP78, an endoplasmic reticulum chaperone immunoglobulin-binding protein [7], which is involved in APP maturation and inhibition of tumour cell growth. In contrast, treating cells with valpromide, a valproate derivative lacking HDAC inhibitory properties, had no effect on APP levels. Valproate did not modify the level of epidermal growth factor receptor, another type I transmembrane protein, nor of APLP2 demonstrating the specificity of the valproate effect on APP. Small interfering RNA-mediated knockdown of APP also resulted in significantly decreased cell growth. Based on these observations, the data suggest that APP down-regulation via HDAC inhibition may provide a novel mechanism for pancreatic and colon cancer therapy. On the other hand, the anti-cancer drug and tyrosine kinase inhibitor, gleevec, stabilises and elevates AICD levels and hence AICD-mediated up-regulation of genes such as *NEP* [82,105]. However, AICD modulation of gene expression appears to be preferentially neuronal specific. For example, AICD is readily detectable in prostate cell lines but does not regulate *NEP* expression except in the presence of HDAC inhibitors [106]. AICD nuclear signalling also does not appear to operate in, for example, endothelial cells, HEK [95], or HeLa cells [96].

Most of the genes identified as AICD targets appear to be up-regulated. However, the epidermal growth factor receptor (EGFR) was shown to be down-regulated following over-expression of AICD whereas deficiency in PS/γ-secretase activity or in APP expression results in a significant increase of EGFR. AICD

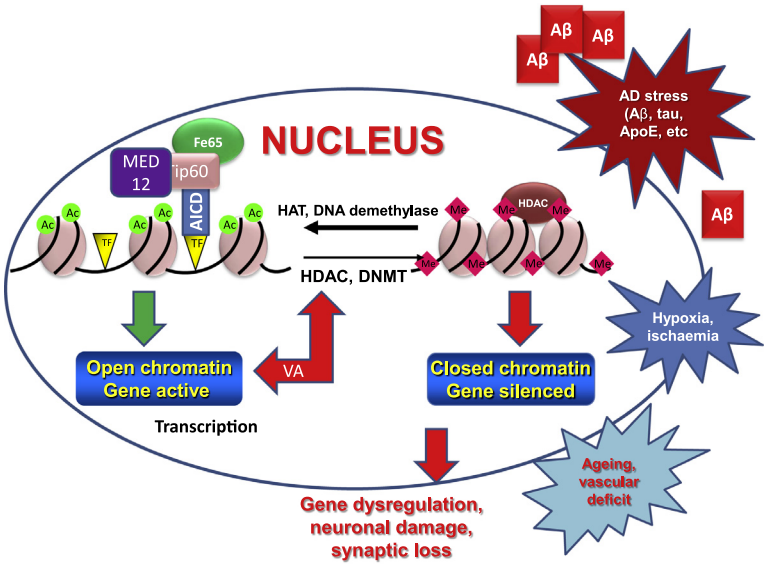

Fig. 3. Role of environmental and stress factors in chromatin remodelling and epigenetic regulation of APP-related gene expression. Binding of HDACs to target gene promoters leads to silencing of the genes while HDAC inhibitors (e.g., valproic acid, VA) facilitate binding of AICD (or other regulators) activating gene expression. Ischaemia, hypoxia, ageing or Aβ-mediated cellular stress result in changes in gene expression leading to synaptic loss and neuronal death.

negatively regulates *EGFR* gene transcription by directly binding to its promoter both in cultured cells and in mouse brain in vivo [107]. Hence AICD may play a role in EGFR-mediated tumorigenesis. The memory loss induced by Aβ oligomers appears to be mediated in part through the EGFR since Aβ oligomers induce EGFR activation suggesting the receptor as a potential target for treating the cognitive dysfunction induced by oligomers [108]. Stathmin-1, which functions as an important regulatory protein of microtubule dynamics and is found associated with neurofibrillary tangles in brains of AD patients, is also down-regulated on AICD overexpression and could contribute to AD pathogenesis [109].

Although AICD over-expression studies need to be treated with caution, it has been demonstrated that such over-expression in mouse neuro2A cells alters the expression of two key signalling proteins, patched homolog 1 (PTCH1), required for sonic hedgehog signalling, and a member of the transient receptor potential cation channel family (TRPC5) [110]. These observations at least suggest a role for AICD in developmental regulation and control of calcium homeostasis.

Comparative transcriptome profiling of *APP* and *APLP2* genes in adult mouse cortex failed, however, to detect changes in some of the previously reported AICD target genes, e.g., *BACE-1, Kai1, GSK-3β* and *p53*, although *EGFR* was up-regulated consistent with the observations of Zhang and colleagues [107] but only modestly in *APLP2*-deficient mice. Some heat shock proteins and plasticity-related genes were both down-regulated in cortices from the APP knockout mice.

AICD may also exert actions independent of direct regulation of gene expression, for example regulation of phosphoinositide-mediated calcium signaling [111]. The apoptotic actions of AICD, particularly when the fragment is over-expressed in vivo or in vitro, may be a consequence of direct interaction with GSK-3β promoting its kinase activity rather than through an effect on its transcription [112,113]. In this way AICD strongly inhibited Wnt/β-catenin-mediated signaling providing the peptide with a regulatory role in neuronal cell proliferation and differentiation.

Also it is not only the C-terminal domain of APP (AICD) that can modulate gene expression. Other metabolites may also have this capability, for example, sAPPβ regulation of the expression of the klotho gene [114]. Even intact APP, quite independent of AICD, has gene regulatory roles, most recently in the demonstration of APP regulation of cholesterol metabolism [115] and of acetylcholinesterase (Hicks D, Makova NZ, Nalivaeva NN, Turner AJ, 2013 in revision). A proteomics study of *APP/APLP1/APLP2* knockdown cell lysates revealed changes to over 30 proteins [116]. In particular, significant down-regulation of methionine adenosyltransferase II suggested a role of APP family proteins in cellular methylation mechanisms and is consistent with reports of disturbed S-adenosylmethionine levels in tissue and CSF of AD patients. Since methylation plays an important role in neurotransmitter metabolism, this may have relevance for neurodegeneration.

7. Unresolved questions and controversies

While the majority of studies into APP biology have focused on pathogenic mechanisms and therapeutic opportunities, a growing number of studies have begun to focus on fundamental physiological roles for APP family members from growth and development to cancer mechanisms. What is clear from this brief overview is that many questions and controversies still, however, remain unresolved. Among those discussed here are the significance of gene regulation by APP and/or its metabolites, particularly the genes regulated by AICD (both up- and down-regulation), the preferred neuronal specificity of these effects and their physiological significance in quantitative terms. The distinct biological functions of the APP isoforms need to be addressed alongside the importance of its homo- and hetero-dimerisation and the roles of the protein domains differentiating the isoforms, especially the KPI region. This may well be important through distinct ligand interactions for the differential trafficking and metabolism of the isoforms. In this context comparative studies of APP_{695} and APLP1 (both lacking the KPI domain) alongside $APP_{751/770}$ and APLP2 (containing KPI domains) could well be informative. The detailed mechanism of AICD transcriptional regulation from its anterograde transport to, and import into, the nucleus, alongside the consensus motifs for AICD-promoter binding need dissecting in detail. Furthermore, the identity of any neuronal "cofactors" required for AICD complex formation and for mediating neuronal specificity need to be identified. More definitive transcriptomic studies are required to identify both APP family regulated genes and the subset of AICD-regulated genes. Overall, AICD modulates both neurotoxic and neuroprotective genes, ranging from Aβ-degrading enzymes to apoptotic genes [40,83]. Hence the peptide mediates a subtle mechanism for the control of gene regulation and its overall contribution to the neurodegenerative pathways needs elucidation, as well as its potential as a therapeutic target.

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