Transcriptional and Post-Transcriptional Regulations of *Amyloid-β Precursor Protein* (*APP*) mRNA

Kaoru Sato[1], Ken-ichi Takayama[1], Makoto Hashimoto[2] and Satoshi Inoue[1]*

[1]*Department of Systems Aging Science and Medicine, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan,* [2]*Department of Basic Technology, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan*

Alzheimer's disease (AD) is an age-associated neurodegenerative disorder characterized by progressive impairment of memory, thinking, behavior, and dementia. Based on ample evidence showing neurotoxicity of amyloid-β (Aβ) aggregates in AD, proteolytically derived from amyloid precursor protein (APP), it has been assumed that misfolding of Aβ plays a crucial role in the AD pathogenesis. Additionally, extra copies of the *APP* gene caused by chromosomal duplication in patients with Down syndrome can promote AD pathogenesis, indicating the pathological involvement of the *APP* gene dose in AD. Furthermore, increased *APP* expression due to locus duplication and promoter mutation of *APP* has been found in familial AD. Given this background, we aimed to summarize the mechanism underlying the upregulation of *APP* expression levels from a cutting-edge perspective. We first reviewed the literature relevant to this issue, specifically focusing on the transcriptional regulation of *APP* by transcription factors that bind to the promoter/enhancer regions. *APP* expression is also regulated by growth factors, cytokines, and hormone, such as androgen. We further evaluated the possible involvement of post-transcriptional regulators of *APP* in AD pathogenesis, such as RNA splicing factors. Indeed, alternative splicing isoforms of *APP* are proposed to be involved in the increased production of Aβ. Moreover, non-coding RNAs, including microRNAs, post-transcriptionally regulate the *APP* expression. Collectively, elucidation of the novel mechanisms underlying the upregulation of *APP* would lead to the development of clinical diagnosis and treatment of AD.

Keywords: amyloid precursor protein, Alzheimer's disease, dementia, transcription, post-transcription, RNA-binding protein, alternative splicing, microRNA

INTRODUCTION

Alzheimer's disease (AD) is the most common form of age-related dementia and a complex neurodegenerative disorder, phenotypically featured with progressive impairment of memory, thinking, and behavior as along with cognitive decline (Bateman et al., 2012; Mucke and Selkoe, 2012; Kirova et al., 2015; Hashimoto et al., 2018). AD is pathologically characterized by the deposition of senile plaques and neurofibrillary tangles (NTFs) in the brain (DeTure and Dickson, 2019). Senile plaques are mainly composed of soluble amyloid-β (Aβ) peptides (Panza et al., 2019), which form aberrant aggregates exhibiting neurotoxicity in the brain; therefore, the crucial role in the AD pathogenesis is assumed to be played by misfolded Aβ, namely amyloid

hypothesis. Notably, NTFs is mainly comprised of a hyperphosphorylated TAU protein, which has been implicated in major neurodegenerative diseases including AD, termed Tauopathy (Panza et al., 2019). Aβ is produced through sequential proteolytic processing of a transmembrane protein, Aβ precursor protein (APP) by the β-site APP-cleaving enzyme 1 (BACE1) and γ-secretase (Panza et al., 2019), through the amyloidogenic pathway. In addition to the amyloidogenic pathway, the majority of APP undergoes non-pathogenic processing mediated by sequential cleavage of α-secretase and γ-secretase (Nguyen, 2019). In this pathway, an N-terminal secreted form of APP (sAPPα) is generated that plays numerous roles in normal physiological functions in the brain, such as neuronal proliferation, differentiation, migration, and synaptic function (Nguyen, 2019; Dar and Glazner, 2020).

To decipher the pathogenesis of AD, several studies have addressed the populations in which genetic variations are known to cause AD. In humans, the *APP* gene is located on chromosome 21 with 18 exons and is alternatively spliced into multiple isoforms, of which three isoforms, APP695, APP751, and APP770 are primarily generated. APP695 is predominantly expressed in neurons, whereas the remainders are expressed rather ubiquitously (Dai et al., 2018). Almost all adults with Down syndrome (DS) display neuropathological changes of AD over 40 years of age due to extra copies of *APP* attributed to the trisomy of chromosome 21 (Wiseman et al., 2015; Antonarakis, 2017; Lott and Head, 2019). Furthermore, a genetic variation observed in individuals with small internal duplications within chromosome 21 can result in three *APP* copies in a rare familial trait known as duplication of *APP* and can lead to an early-onset AD (Rovelet-Lecrux et al., 2006; Sleegers et al., 2006; Kasuga et al., 2009; Thonberg et al., 2011; Hooli et al., 2012; Swaminathan et al., 2012). In contrast, partial trisomy of chromosome 21 lacking an extra copy of the *APP* gene does not promote AD (Prasher et al., 1998; Korbel et al., 2009). The *APP* copy number is also mosaically amplified in the neurons of late-onset sporadic AD brains (Bushman et al., 2015). Additionally, genomic variations within *APP* promoter can upregulate its expression thereby increasing the risk of AD (Prasher et al., 1998; Guyant-Maréchal et al., 2007). This implies that the genetic variations involving an increase in *APP* mRNA levels are associated with AD pathophysiology. Moreover, increased *APP* expression levels have been detected in the brain, particularly in the entorhinal cortex neurons containing neurofibrillary tangles in AD patients (Cohen et al., 1988; Higgins et al., 1988; Guttula et al., 2012). Together, *APP* expression levels can impact the pathological processes in AD. Here, we summarized the literature relevant to this issue, specifically focusing on both transcriptional and post-transcriptional regulation of *APP* mRNA, and examined their roles in AD pathogenesis.

TRANSCRIPTIONAL REGULATION OF *APP*

In this section, we summarized the annotated genomic features of the human *APP* promoter/enhancer and its transcriptional regulators.

APP Promoter/Enhancer Activity

The promoter of the human *APP* lacks TATA and CAAT boxes upstream of the transcription start site but contains a high GC region with five GGGCGC boxes (Lahiri and Robakis, 1991) (**Figure 1A**), which adapts to the typical characteristics of a housekeeping gene (Smale and Kadonaga, 2003). The proximal region of the promoter from –150 to –10 base pairs (bp) contains the minimum essential elements for *APP* promoter activity (Lahiri and Robakis, 1991; Lahiri and Nall, 1995). The region from –600 to –460 bp acts as a transcriptionally positive regulator; in particular, a 26 bp positioned between –489 and –462 bp acts as a strong enhancer. In contrast, the region from –450 to –150 bp works as a negative regulator. Additionally, the downstream region of the *APP* promoter does not match the consensus sequences for any of the downstream core promoter sequences, such as the downstream promoter element (DPE), which is generally required for efficient transcription (Vostrov et al., 2010). However, the region from +72 to +115 has an unknown nuclear factor-binding domain termed as DNase I protected domain (DAPB), which is required for *APP* promoter activity in HeLa cells.

Stimulating Protein 1 (SP-1)

SP-1 belongs to the Sp/KLF family of transcription factors and directly binds to the DNA sequence by its own zinc finger motif to enhance gene transcription in response to oxidative stress and hypoxia (Yeh et al., 2011). Indeed, SP-1 binds to the *APP* promoter (**Figure 1A** and **Table 1**) and accelerates the production of *APP* transcripts (Pollwein, 1993; Hattori et al., 1997; Basha et al., 2005). The SP-1 binding site partially overlaps with the *APP* promoter binding α (APBα) domain (**Figure 1A**), an intact nuclear factor-binding site essential for *APP* transcription. Additionally, the upstream transcription factor (USF), a basic helix-loop-helix transcription factor, also binds to the APBα domain Vostrov et al. (1995) and contributes to an increased *APP* expression in neurons (Yang et al., 1999).

Activator Protein-1 (AP-1)

AP-1 is a heterodimer composed of proteins belonging to the c-Fos, c-Jun, activating transcription factors (ATFs), and Jun dimerization protein (JDP) families (Shaulian and Karin, 2002). AP-1 regulates gene expression in response to numerous stimuli, including cytokines, growth factors, and stress (Shaulian and Karin, 2002; Hess et al., 2004). Although two putative AP-1 recognition sites are located at the *APP* promoter, the distal AP-1 recognition site alone is sufficient for transcriptional activation by AP-1, such as c-Fos/-Jun heterodimer, rather than the proximal site (Trejo et al., 1994; Lahiri and Ge, 2004) (**Figure 1A** and **Table 1**).

CCCTC-Binding Factor (CTCF) and Transforming Growth Factor-β (TGF-β)

CTCF is generally a multifunctional positive or negative regulator of various target genes and plays a key role in transcriptional insulation (Quitschke et al., 2000). CTCF contains tandem 11 zinc finger motifs, of which five to seven zinc fingers are required for binding to positions –98 and –83 bp of the human *APP* promoter, which was formerly designated as APBβ, another intact
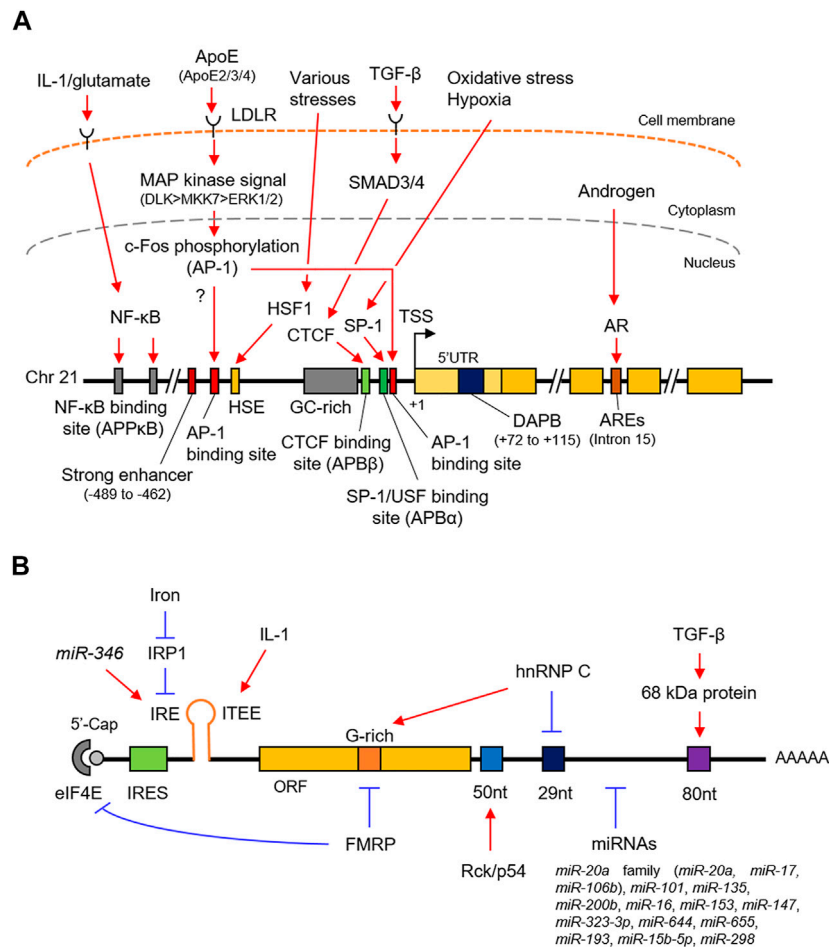
FIGURE 1 | Schematic representation of the transcriptional and post-transcriptional regulation of *APP*. **(A)**. The promoter structure and regulating factors for the *APP* transcription. **(B)**. *cis*-regulatory elements and *trans*-acting factors for the post-transcriptional regulation. *APP*, amyloid-β precursor protein; SP-1, putative SP-1 binding site; AP-1, putative AP-1 binding site; HSP, heat shock element; DAPB, DNase I protected domain; ARE, androgen response element; AR, androgen receptor. IRES, internal ribosome entry site; IRE, iron responsive element; ITEE, interleukin-1 translation enhancer element; IRP1, iron response protein 1; 52 nt, 52 nt element; 29 nt, 29 nt element; 80 nt, 80 nt element.

nuclear factor-binding site essential for *APP* transcription (Quitschke and Goldgaber, 1992; Quitschke, 1994; Quitschke et al., 2000) (**Figure 1A** and **Table 1**). APBβ is also responsive to TGF-β, a multifunctional cytokine, in which two TGF-β signaling mediators, mothers against decapentaplegic homolog 3 (SMAD3) and SMAD4, associate with CTCF on the APBβ and promote *APP* transcription in cooperation with SP-1 (Burton et al., 2002; Docagne et al., 2004).

TGF-β is also implicated in the post-transcriptional regulation of *APP*. A TGF-β-responsive protein forms a 68 kDa RNA-protein complex and is proposed to stabilize the *APP* transcript by binding to the 81 nt sequence within the *APP* 3′UTR, increasing its translation (Amara et al., 1999; Westmark and Malter, 2012).

Heat Shock Transcription Factor 1 (HSF-1)

The transcription of *APP* is stimulated by various stress factors such as heat shock and treatment with ethanol and arsenite (Dewji et al., 1995). The HSF1 binds to the heat shock element (HSE) of the *APP* promoter (Dewji and Do, 1996)

(**Figure 1A** and **Table 1**). It acts as a primary mediator of stress-responsive transcription of pro-survival genes, including heat shock proteins (Akerfelt et al., 2010). Under normal conditions, HSF1 is predominantly localized in the cytoplasm in a repressed monomeric form. Upon stress, HSF1 trimerizes and accumulates in the nucleus, where it binds to HSE.

Nuclear Factor (NF)-κB/Rel

The NF-κB transcription factor forms a dimer composed of NF-κB/Rel family subunits including NF-κB1/p50 and regulates transcription of genes involved in immune and inflammatory responses in response to stimuli such as inflammation and disease (Dresselhaus and Meffert, 2019). NF-κB1/p50-containing complex, widely expressed in neurons and glial cells in the human brain, is activated through the canonical NF-κB pathway extracellularly stimulated by cytokines and neurotransmitter in neurons, where it plays important roles for neuroprotective functions including anti-apoptosis under the neurodegenerative condition, but not well-defined in glial cells. To activate *APP*

TABLE 1 | List of transcriptional and post-transcriptional regulators for the *APP* expression.

Name	Mechanism	*APP* level	References
Transcription			
SP-1	Activate *APP* transcription through binding to the SP-1 element within the *APP* promoter	Up	Lahiri and Robakis, (1991) Pollwein, (1993) Lahiri and Nall, (1995) Hattori et al. (1997)
AP-1	Activate *APP* transcription through binding to the AP-1 element within the *APP* promoter	Up	Trejo et al. (1994) Lahiri and Ge, (2004)
CTCF	Activate *APP* transcription through binding to the APBβ domain within the *APP* promoter	Up	Quitschke and Goldgaber, (1992) Quitschke, (1994) Quitschke et al. (2000)
HSF1	In response to stress, activate *APP* transcription through binding to the HSE within the *APP* promoter	Up	Dewji et al. (1995) Dewji and Do, (1996)
NF-κB/Rel	Activate *APP* transcription through binding to two binding motifs at the distal *APP* promoter	Up	Grilli et al. (1995) Grilli et al. (1996)
USF	Activate *APP* transcription through binding to the APBα domain within the *APP* promoter	Up	Vostrov et al. (1995) Yang et al. (1999)
Androgen	Activate *APP* transcription through binding to ARE within the *APP* intron	Up	Takayama et al. (2009) Takayama et al. (2019)
ApoE	Activate MAP kinase signal and c-Fos phosphorylation (AP-1)	Up	Huang et al. (2017)
Post-transcription			
Iron	Dissociate IRP1 from IRE by binding, eliciting the *APP* translation	Down	Rogers et al. (2008) Cho et al. (2010)
IL-1	Bind to the IL-1 translational enhancer element at the *APP* 5′UTR, increasing its stability	Up	Rogers et al. (1999)
TGF-β	Modulate the 81 nt element-mediated stabilization of *APP* mRNA	Up	Amara et al. (1999)
FMRP	Bind to the G-rich motif, inhibiting the *APP* translation Inhibit eIF4E with CYFIP1	Down	Westmark and Malter, (2007) Napoli et al. (2008)
hnRNP C	Bind to the G-rich motif and the 29 nt element, increasing the *APP* mRNA stability	Up	Rajagopalan et al. (1998)
Rck/p54	Bind to the 52 nt element, increasing the *APP* mRNA stability	Up	Broytman et al. (2009)
PSF/SFPQ	Stabilize *APP* mRNA through interaction	Up	Takayama et al. (2019)
miR-106a (*)	Bind to 3′UTR of *APP* transcript, and lead the miRNA-mediated repression	Down	Patel et al. (2008)
miR-520c (*)			Hébert et al. (2009)
miR-20a family (miR-20a, miR-17, miR-106b) (*)			Vilardo et al. (2010)
miR-101 (*)			Delay et al. (2011)
miR-135 (*)			Long and Lahiri, (2011)
miR-200b (*)			Liang et al. (2012)
miR-193 (*)			Long et al. (2012)
miR-298 (*)			Barbato et al. (2014)
miR-16			Liu et al. (2014a)
miR-153			Liu et al. (2014b)
miR-147			Galimberti et al. (2014)
miR-323-3p			Zhang et al. (2015)
miR-644			Liu et al. (2019)
miR-655			Chopra et al. (2020)
miR-15b-5p			
miR-346 (*)	Bind to IRE in the *APP* 5′UTR and upregulate its translation	Up	Long et al. (2019)

Asterisk (*) indicates miRNA of which functional involvement has been investigated using human brain tissue or neuronal cells.

transcription, the NF-κB1/p50-containing complex specifically recognize APPκB sites in the distal *APP* promoter, where IL-1 and glutamate enhance its binding activity (Grilli et al., 1995; Grilli et al., 1996) (**Figure 1A** and **Table 1**).

Androgen

Androgens are natural steroid hormones that regulate various physiological phenomena taking place in several tissues and organs, including the brain, by binding to the androgen receptor (AR), a member of the nuclear receptor superfamily (Chang et al., 2013; Takayama and Inoue, 2013). After ligand binding, the AR homodimer translocates into the nucleus, where it binds to the androgen-responsive element (ARE), and subsequently activates gene expression often with epigenetic changes in the chromatin state (Tewari et al., 2012; Nevedomskaya et al., 2016; Nadal et al., 2017; Stelloo et al., 2019). *APP* is a primary androgen-regulated gene in human neuronal and prostate cancer cells (Takayama et al., 2009; Takayama et al., 2019). In neurons, AR directly binds to the ARE located within the genomic regions corresponding to the 15th intron of the *APP* gene (Takayama et al., 2019) (**Figure 1A** and **Table 1**). Notably, the chromatin binding level of histone H3

acetylated at lysine 9 (H3K9ac), a transcriptionally active histone mark, at the *APP* promoter is enhanced with overexpression of AR. Importantly, the androgen concentration declines with age in serum and brain (Rosario et al., 2011; Grimm et al., 2016; Gaignard et al., 2017) and is likely associated with AD development (Gouras et al., 2000; Wahjoepramono et al., 2008; César et al., 2016; Jayadevappa et al., 2019).

Apolipoprotein E (ApoE)

ApoE is a major component of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). It acts on the metabolism of fats, including the transportation of lipids, fat-soluble vitamins, and cholesterol into the lymph and blood by binding to the LDL receptor (LDLR) (Goldstein and Brown, 2015). Although it is largely synthesized in the liver, the elevated expression has also been characterized in the brain, primarily in the astrocytes (Holtzman et al., 2012; Wang and Eckel, 2014). Humans harbor three major ApoE alleles: ApoE-ε2, ApoE-ε3, and ApoE-ε4 (Ghebranious et al., 2005; Eisenberg et al., 2010). Importantly, ApoE-ε4 is a well-known genetic risk factor for atherosclerosis and AD in the brain, unlike ApoE-ε2 and ApoE-ε3 (Strittmatter et al., 1993; Farrer et al., 1997; Huang et al., 2017). In the human brain, ApoE proteins secreted from the glia stimulate *APP* transcription and Aβ production with different efficacy in the neurons (Huang et al., 2017; Vogrinc et al., 2021). In this pathway, secreted ApoE protein binds to the LDLR on the neuron surfaces and activates a non-canonical MAP kinase signaling pathway mediated by DLK, MKK7, and ERK1/2 (**Figure 1A** and **Table 1**). Subsequently, c-Fos, a subunit of AP-1, is phosphorylated (Shaulian and Karin, 2002), in turn enhances AP-1–dependent *APP* transcription (Huang et al., 2017). Notably, ApoE-ε4 is also involved in the recognition and engulfing of Aβ in the brain (Strittmatter et al., 1993; Farrer et al., 1997).

POST-TRANSCRIPTIONAL REGULATION OF *APP*

We have reviewed the *cis*-regulatory elements of the *APP* transcript and *trans*-acting factors for the post-transcriptional regulation of *APP*.

Iron

The *APP* 5′untranslated region (UTR) contains an internal ribosome entry site (IRES), an iron-responsive element (IRE), and an interleukin-1 (IL-1) translation enhancer element (**Figure 1B** and **Table 1**). The IRES is a specialized RNA element that allows the recruitment of eukaryotic ribosomes to mRNA, regardless of the presence of the 5′cap (Hellen and Sarnow, 2001; López-Lastra et al., 2005); therefore, endogenous *APP* is translated in a cap-independent manner (Beaudoin et al., 2008). In the absence of iron, iron response protein 1 (IRP1), an iron-dependent translational repressor, is presumed to bind to the IRE of the *APP* transcript. This prevents the recruitment of the 40 S ribosome at the 5'cap, subsequently repressing the translation (Rogers et al., 2008; Cho et al., 2010).

Interleukin-1 (IL-1)

An IL-1 translation enhancer element (ITEE), also known as IL-1 acute box, is present close to IRE, (Rogers et al., 2002; Rogers et al., 2008; Ruberti et al., 2010; Bandyopadhyay et al., 2013) (**Figure 1B** and **Table 1**). IL-1α and IL-1β, are a group of IL-1 cytokines that play a crucial role in regulating immune and inflammatory responses to not only infections but also in all inflammatory, physiological or pathological phenomena (Dinarello, 2018; Kaneko et al., 2019). It is also known to be increased in the brains of AD patients (Cacabelos et al., 1994; Shaftel et al., 2008; Italiani et al., 2018). Using CAT assay, a 90 nt element in the *APP* 5′UTR, which includes the enhancer element, was found to enhance its translation without changing the steady-state mRNA level (Rogers et al., 1999; Westmark and Malter, 2012), indicating that IL-1 post-transcriptionally upregulates *APP* translation.

Fragile X Mental Retardation Protein (FMRP)

The protein-coding region of *APP* contains a G-rich motif that interacts with the FMRP (**Figure 1B** and **Table 1**) which is highly expressed in the brain. Loss of FMRP causes fragile X syndrome, largely characterized by cognitive impairment (O'Donnell and Warren, 2002). FMRP associates with the *APP* transcript *via* its own multiple RNA-binding motifs such as KH motif and RGG box to repress the translation of *APP* in a type 1 metabotropic glutamate receptor (mGluR)-dependent manner; thus, stimulation of mGluR elicits an increase in the *APP* translation (Westmark and Malter, 2007). In addition, FMRP interacts with cytoplasmic FMR1–interacting protein 1 (CYFIP1), thereby inhibiting *APP* translation by sequestering eukaryotic initiation factor 4E (eIF4E) (Napoli et al., 2008). Notably, loss of FMRP results in the production of excess soluble APP, which contributes to a deficiency in dendrite maturation (Pasciuto et al., 2015). Normalizing *APP* levels in Fmrp-knockout mice can rescue the fragile X phenotypes (Westmark et al., 2011), indicating the importance of *APP* homeostasis in the development of this disorder.

Heterogeneous Nuclear Ribonucleoprotein C (hnRNP C)

It has been reported that hnRNP C, a ubiquitous RNA regulatory protein, competitively binds to the same G-rich motif as FMRP (**Figure 1B** and **Table 1**). It harbors an RNA recognition motif (RRM) and is associated with pre-mRNAs to regulate RNA processing, metabolism, and transport (Piñol-Roma and Dreyfuss, 1993; Han et al., 2010). In contrast to FMRP, hnRNP C enhances *APP* translation by binding to the G-rich motif. Additionally, hnRNP C also binds to the repressive 29 nt element in the *APP* 3′UTR, thereby increasing its stability (Rajagopalan et al., 1998).

Rck/p54

Rck/p54, a member of the DEAD-box family of RNA helicases is also known as DEAD-box helicase 6 (DDX6). Rck/p54 modulates

mRNA secondary structures Akao et al. (1995) by binding to the 52 nt elements downstream of the stop codon and increasing *APP* mRNA stability (Broytman et al., 2009) (**Figure 1B** and **Table 1**). Indeed, the helicase activity of Rck/p54 is required for *APP* mRNA stability.

Polypyrimidine Tract-Binding Protein-Associated Splicing Factor/Splicing Factor Proline- and Glutamine-Rich (PSF/SFPQ)

PSF, also known as SFPQ, is a ubiquitously expressed nuclear RNA-binding protein (RBP) (Knott et al., 2016). PSF/SFPQ is mainly localized at the nucleus, in particular to the membraneless condensates known as paraspeckles, in which nuclear enriched abundant transcript 1 (NEAT1), an architectural long non-coding RNA, is bound to core proteins, including PSF/SFPQ. The latter regulates various cellular mechanisms such as alternative splicing and nuclear retention of mRNAs (Nakagawa et al., 2018; Lim et al., 2020). Importantly, PSF/SFPQ plays a critical role in neural development as well as in neurodegenerative diseases, including AD (Ke et al., 2012; Lu et al., 2018; Younas et al., 2020). It directly binds to the primary *APP* transcripts in human neuronal cells, leading to *APP* mRNA stabilization (Takayama et al., 2019) (**Figure 1B** and **Table 1**).

microRNA (miRNA)

RNA silencing is a nucleotide-sequence-specific regulation of gene expression mediated by small non-coding RNAs such as miRNAs (Ghildiyal and Zamore, 2009; Kim et al., 2009; Czech and Hannon, 2011). In most cases, miRNAs interact with the 3′UTR of target mRNAs to induce their degradation by mRNA decay or inhibit their translation. In recent years, several miRNAs have been identified to participate in AD pathogenesis by regulating the expression of multiple target genes, including *APP*. miR-106a and miR-520c were the first miRNAs experimentally demonstrated to downregulate *APP* levels post-transcriptionally (Patel et al., 2008). In subsequent studies, further 15 miRNAs, as listed in **Table 1**, have been identified to bind directly to the 3′UTR of the human *APP* transcript and downregulate its expression at the post-transcriptional level. Unlike most miRNAs, miR-346 interacts with the *APP* 5′UTR to promote translation (Long et al., 2019) (**Figure 1B**). The miR-346 target site overlaps with the IRE at the *APP* 5′UTR, where miR-346 would displace IRP1 even at low iron levels, eliciting *APP* translation, suggesting that miR-346

may maintain *APP* homeostasis and prevent the pathogenic *APP* cascade in AD.

CONCLUSION

Here, we summarized multiple regulatory mechanisms of *APP* mRNA at the transcriptional and post-transcriptional levels, particularly in the human brain. An imbalance in *APP* levels caused by aberrancy of these mechanisms can trigger increased AD development, as mentioned above.

PERSPECTIVE

Immunotherapy against ApoE improves amyloid-associated phenotypes rather than Aβ (Xiong et al., 2021), suggesting elucidation of the regulatory mechanisms of *APP* expression can provide effective therapeutic strategies to interrupt the development or further progression of AD. Moreover, recent advances in high-throughput sequencing technologies have facilitated the reconstruction of the entire transcriptional landscape and RNA–RBP networks in human diseases. In addition, more recently, RBPs such as transactive response DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS) related to neurodegenerative diseases have been shown to undergo liquid-liquid phase separation (LLPS). Aberrant phase transitions of these RBPs in the brain lead to the disorder (Patel et al., 2015; Wolozin and Ivanov, 2019; Boyko et al., 2020), suggesting a possible role of LLPS in AD-related RBPs in *APP* homeostasis.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

REFERENCES

Akao, Y., Marukawa, O., Morikawa, H., Nakao, K., Kamei, M., Hachiya, T., et al. (1995). The Rck/p54 Candidate Proto-Oncogene Product Is a 54-kilodalton D-E-A-D Box Protein Differentially Expressed in Human and Mouse Tissues. *Cancer Res.* 55, 3444–3449.

Åkerfelt, M., Morimoto, R. I., and Sistonen, L. (2010). Heat Shock Factors: Integrators of Cell Stress, Development and Lifespan. *Nat. Rev. Mol. Cel. Biol.* 11, 545–555. doi:10.1038/nrm2938

Amara, F. M., Junaid, A., Clough, R. R., and Liang, B. (1999). TGF-β1, Regulation of Alzheimer Amyloid Precursor Protein mRNA Expression in a normal Human Astrocyte Cell Line: mRNA Stabilization. *Mol. Brain Res.* 71, 42–49. doi:10.1016/s0169-328x(99)00158-8

Antonarakis, S. E. (2017). Down Syndrome and the Complexity of Genome Dosage Imbalance. *Nat. Rev. Genet.* 18, 147–163. doi:10.1038/nrg.2016.154

Bandyopadhyay, S., Cahill, C., Balleidier, A., Huang, C., Lahiri, D. K., Huang, X., et al. (2013). Novel 5′ Untranslated Region Directed Blockers of Iron-Regulatory Protein-1 Dependent Amyloid Precursor Protein Translation:

Implications for Down Syndrome and Alzheimer's Disease. *PLoS One* 8, e65978. doi:10.1371/journal.pone.0065978

Barbato, C., Pezzola, S., Caggiano, C., Antonelli, M., Frisone, P., Ciotti, M. T., et al. (2014). A Lentiviral Sponge for miR-101 Regulates RanBP9 Expression and Amyloid Precursor Protein Metabolism in Hippocampal Neurons. *Front. Cel. Neurosci.* 8, 37. doi:10.3389/fncel.2014.00037

Basha, M. R., Wei, W., Bakheet, S. A., Benitez, N., Siddiqi, H. K., Ge, Y. W., et al. (2005). The Fetal Basis of Amyloidogenesis: Exposure to Lead and Latent Overexpression of Amyloid Precursor Protein and -Amyloid in the Aging Brain. *J. Neurosci.* 25, 823–829. doi:10.1523/JNEUROSCI.4335-04.2005

Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., et al. (2012). Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *N. Engl. J. Med.* 367, 795–804. doi:10.1056/NEJMoa1202753

Beaudoin, M. E., Poirel, V.-J., and Krushel, L. A. (2008). Regulating Amyloid Precursor Protein Synthesis through an Internal Ribosomal Entry Site. *Nucleic Acids Res.* 36, 6835–6847. doi:10.1093/nar/gkn792

Boyko, S., Surewicz, K., and Surewicz, W. K. (2020). Regulatory Mechanisms of Tau Protein Fibrillation under the Conditions of Liquid-Liquid Phase Separation. *Proc. Natl. Acad. Sci. USA* 117, 31882–31890. doi:10.1073/pnas.2012460117

Broytman, O., Westmark, P. R., Gurel, Z., and Malter, J. S. (2009). Rck/p54 Interacts with APP mRNA as Part of a Multi-Protein Complex and Enhances APP mRNA and Protein Expression in Neuronal Cell Lines. *Neurobiol. Aging* 30, 1962–1974. doi:10.1016/j.neurobiolaging.2008.02.011

Burton, T., Liang, B., Dibrov, A., and Amara, F. (2002). Transforming Growth Factor-β-Induced Transcription of the Alzheimer β-amyloid Precursor Protein Gene Involves Interaction between the CTCF-Complex and Smads. *Biochem. Biophysical Res. Commun.* 295, 713–723. doi:10.1016/s0006-291x(02)00725-8

Bushman, D. M., Kaeser, G. E., Siddoway, B., Westra, J. W., Rivera, R. R., Rehen, S. K., et al. (2015). Genomic Mosaicism with Increased Amyloid Precursor Protein (APP) Gene Copy Number in Single Neurons from Sporadic Alzheimer's Disease Brains. *Elife* 4, e05116. doi:10.7554/eLife.05116

Cacabelos, R., Alvarez, X. A., Fernández-Novoa, L., Franco, A., Mangues, R., Pellicer, A., et al. (1994). Brain Interleukin-1 Beta in Alzheimer's Disease and Vascular Dementia. *Methods Find Exp. Clin. Pharmacol.* 16, 141–151.

César, K. G., Brucki, S. M. D., Takada, L. T., Nascimento, L. F. C., Gomes, C. M. S., Almeida, M. C. S., et al. (2016). Prevalence of Cognitive Impairment without Dementia and Dementia in Tremembé, Brazil. *Alzheimer Dis. Assoc. Disord.* 30, 264–271. doi:10.1097/WAD.0000000000000122

Chang, C., Yeh, S., Lee, S. O., and Chang, T.-m. (2013). Androgen Receptor (AR) Pathophysiological Roles in Androgen Related Diseases in Skin, Metabolism Syndrome, Bone/Muscle and Neuron/Immune Systems: Lessons Learned from Mice Lacking AR in Specific Cells. *Nucl. Recept. Signal.* 11, nrs.11001–e001. doi:10.1621/nrs.11001

Cho, H.-H., Cahill, C. M., Vanderburg, C. R., Scherzer, C. R., Wang, B., Huang, X., et al. (2010). Selective Translational Control of the Alzheimer Amyloid Precursor Protein Transcript by Iron Regulatory Protein-1. *J. Biol. Chem.* 285, 31217–31232. doi:10.1074/jbc.M110.149161

Chopra, N., Wang, R., Maloney, B., Nho, K., Beck, J. S., Pourshafie, N., et al. (2020). MicroRNA-298 Reduces Levels of Human Amyloid-β Precursor Protein (APP), β-site APP-Converting Enzyme 1 (BACE1) and Specific Tau Protein Moieties. *Mol. Psychiatry.* doi:10.1038/s41380-019-0610-2

Cohen, M. L., Golde, T. E., Usiak, M. F., Younkin, L. H., and Younkin, S. G. (1988). *In Situ* hybridization of Nucleus Basalis Neurons Shows Increased Beta-Amyloid mRNA in Alzheimer Disease. *Proc. Natl. Acad. Sci.* 85, 1227–1231. doi:10.1073/pnas.85.4.1227

Czech, B., and Hannon, G. J. (2011). Small RNA Sorting: Matchmaking for Argonautes. *Nat. Rev. Genet.* 12, 19–31. doi:10.1038/nrg2916

Dai, M.-H., Zheng, H., Zeng, L.-D., and Zhang, Y. (2018). The Genes Associated with Early-Onset Alzheimer's Disease. *Oncotarget* 9, 15132–15143. doi:10.18632/oncotarget.23738

Dar, N. J., and Glazner, G. W. (2020). Deciphering the Neuroprotective and Neurogenic Potential of Soluble Amyloid Precursor Protein Alpha (sAPPα). *Cell. Mol. Life Sci.* 77, 2315–2330. doi:10.1007/s00018-019-03404-x

Delay, C., Calon, F., Mathews, P., and Hébert, S. S. (2011). Alzheimer-specific Variants in the 3′UTR of Amyloid Precursor Protein Affect microRNA Function. *Mol. Neurodegeneration* 6, 70. doi:10.1186/1750-1326-6-70

DeTure, M. A., and Dickson, D. W. (2019). The Neuropathological Diagnosis of Alzheimer's Disease. *Mol. Neurodegeneration* 14, 32. doi:10.1186/s13024-019-0333-5

Dewji, N. N., Do, C., and Bayney, R. M. (1995). Transcriptional Activation of Alzheimer's β-amyloid Precursor Protein Gene by Stress. *Mol. Brain Res.* 33, 245–253. doi:10.1016/0169-328x(95)00131-b

Dewji, N. N., and Do, C. (1996). Heat Shock Factor-1 Mediates the Transcriptional Activation of Alzheimer's β-amyloid Precursor Protein Gene in Response to Stress. *Mol. Brain Res.* 35, 325–328. doi:10.1016/0169-328x(95)00214-d

Dinarello, C. A. (2018). Overview of the IL-1 Family in Innate Inflammation and Acquired Immunity. *Immunol. Rev.* 281, 8–27. doi:10.1111/imr.12621

Docagne, F., Gabriel, C., Lebeurrier, N., Lesné, S., Hommet, Y., Plawinski, L., et al. (2004). Sp1 and Smad Transcription Factors Co-operate to Mediate TGF-β-dependent Activation of Amyloid-β Precursor Protein Gene Transcription. *Biochem. J.* 383, 393–399. doi:10.1042/BJ20040682

Dresselhaus, E. C., and Meffert, M. K. (2019). Cellular Specificity of NF-Kb Function in the Nervous System. *Front. Immunol.* 10, 1043. doi:10.3389/fimmu.2019.01043

Eisenberg, D. T. A., Kuzawa, C. W., and Hayes, M. G. (2010). Worldwide Allele Frequencies of the Human Apolipoprotein E Gene: Climate, Local Adaptations, and Evolutionary History. *Am. J. Phys. Anthropol.* 143, 100–111. doi:10.1002/ajpa.21298

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., et al. (1997). Effects of Age, Sex, and Ethnicity on the Association between Apolipoprotein E Genotype and Alzheimer Disease. A Meta-Analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 278, 1349–1356. doi:10.1001/jama.278.16.1349

Gaignard, P., Liere, P., Thérond, P., Schumacher, M., Slama, A., and Guennoun, R. (2017). Role of Sex Hormones on Brain Mitochondrial Function, with Special Reference to Aging and Neurodegenerative Diseases. *Front. Aging Neurosci.* 9, 406. doi:10.3389/fnagi.2017.00406

Galimberti, D., Villa, C., Fenoglio, C., Serpente, M., Ghezzi, L., Cioffi, S. M. G., et al. (2014). Circulating miRNAs as Potential Biomarkers in Alzheimer's Disease. *Jad* 42, 1261–1267. doi:10.3233/JAD-140756

Ghebranious, N., Ivacic, L., Mallum, J., and Dokken, C. (2005). Detection of ApoE E2, E3 and E4 Alleles Using MALDI-TOF Mass Spectrometry and the Homogeneous Mass-Extend Technology. *Nucleic Acids Res.* 33, e149. doi:10.1093/nar/gni155

Ghildiyal, M., and Zamore, P. D. (2009). Small Silencing RNAs: an Expanding Universe. *Nat. Rev. Genet.* 10, 94–108. doi:10.1038/nrg2504

Goldstein, J. L., and Brown, M. S. (2015). A century of Cholesterol and Coronaries: from Plaques to Genes to Statins. *Cell* 161, 161–172. doi:10.1016/j.cell.2015.01.036

Gouras, G. K., Xu, H., Gross, R. S., Greenfield, J. P., Hai, B., Wang, R., et al. (2000). Testosterone Reduces Neuronal Secretion of Alzheimer's Beta -amyloid Peptides. *Proc. Natl. Acad. Sci.* 97, 1202–1205. doi:10.1073/pnas.97.3.1202

Grilli, M., Goffi, F., Memo, M., and Spano, P. (1996). Interleukin-1β and Glutamate Activate the NF-κB/Rel Binding Site from the Regulatory Region of the Amyloid Precursor Protein Gene in Primary Neuronal Cultures. *J. Biol. Chem.* 271, 15002–15007. doi:10.1074/jbc.271.25.15002

Grilli, M., Ribola, M., Alberici, A., Valerio, A., Memo, M., and Spano, P. (1995). Identification and Characterization of a κB/Rel Binding Site in the Regulatory Region of the Amyloid Precursor Protein Gene. *J. Biol. Chem.* 270, 26774–26777. doi:10.1074/jbc.270.45.26774

Grimm, A., Mensah-Nyagan, A. G., and Eckert, A. (2016). Alzheimer, Mitochondria and Gender. *Neurosci. Biobehavioral Rev.* 67, 89–101. doi:10.1016/j.neubiorev.2016.04.012

Guttula, S. V., Allam, A., and Gumpeny, R. S. (2012). Analyzing Microarray Data of Alzheimer's Using Cluster Analysis to Identify the Biomarker Genes. *Int. J. Alzheimers Dis.* 2012, 649456. doi:10.1155/2012/649456

Guyant-Maréchal, L., Rovelet-Lecrux, A., Goumidi, L., Cousin, E., Hannequin, D., Raux, G., et al. (2007). Variations in the APP Gene Promoter Region and Risk of Alzheimer Disease. *Neurology* 68, 684–687. doi:10.1212/01.wnl.0000255938.33739.46

Han, S. P., Tang, Y. H., and Smith, R. (2010). Functional Diversity of the hnRNPs: Past, Present and Perspectives. *Biochem. J.* 430, 379–392. doi:10.1042/BJ20100396

Hashimoto, M., Ho, G., Sugama, S., Takamatsu, Y., Shimizu, Y., Takenouchi, T., et al. (2018). Evolvability of Amyloidogenic Proteins in Human Brain. *J. Alzheimers Dis.* 62, 73–83. doi:10.3233/JAD-170894

Hattori, M., Tsukahara, F., Furuhata, Y., Tanahashi, H., Hirose, M., Saito, M., et al. (1997). A Novel Method for Making Nested Deletions and its Application for Sequencing of a 300 Kb Region of Human APP Locus. *Nucleic Acids Res.* 25, 1802–1808. doi:10.1093/nar/25.9.1802

Hébert, S. S., Horré, K., Nicolaï, L., Bergmans, B., Papadopoulou, A. S., Delacourte, A., et al. (2009). MicroRNA Regulation of Alzheimer's Amyloid Precursor Protein Expression. *Neurobiol. Dis.* 33, 422–428. doi:10.1016/j.nbd.2008.11.009

Hellen, C. U. T., and Sarnow, P. (2001). Internal Ribosome Entry Sites in Eukaryotic mRNA Molecules. *Genes Dev.* 15, 1593–1612. doi:10.1101/gad.891101

Hess, J., Angel, P., and Schorpp-Kistner, M. (2004). AP-1 Subunits: Quarrel and harmony Among Siblings. *J. Cel. Sci.* 117, 5965–5973. doi:10.1242/jcs.01589

Higgins, G. A., Lewis, D. A., Bahmanyar, S., Goldgaber, D., Gajdusek, D. C., Young, W. G., et al. (1988). Differential Regulation of Amyloid-Beta-Protein mRNA Expression within Hippocampal Neuronal Subpopulations in Alzheimer Disease. *Proc. Natl. Acad. Sci.* 85, 1297–1301. doi:10.1073/pnas.85.4.1297

Holtzman, D. M., Herz, J., and Bu, G. (2012). Apolipoprotein E and Apolipoprotein E Receptors: normal Biology and Roles in Alzheimer Disease. *Cold Spring Harbor Perspect. Med.* 2, a006312. doi:10.1101/cshperspect.a006312

Hooli, B. V., Mohapatra, G., Mattheisen, M., Parrado, A. R., Roehr, J. T., Shen, Y., et al. (2012). Role of Common and Rare APP DNA Sequence Variants in Alzheimer Disease. *Neurology* 78, 1250–1257. doi:10.1212/WNL.0b013e3182515972

Huang, Y.-W. A., Zhou, B., Wernig, M., and Südhof, T. C. (2017). ApoE2, ApoE3, and ApoE4 Differentially Stimulate APP Transcription and Aβ Secretion. *Cell* 168, 427–441.e21. doi:10.1016/j.cell.2016.12.044

Italiani, P., Puxeddu, I., Napoletano, S., Scala, E., Melillo, D., Manocchio, S., et al. (2018). Circulating Levels of IL-1 Family Cytokines and Receptors in Alzheimer's Disease: New Markers of Disease Progression?. *J. Neuroinflammation* 15, 342. doi:10.1186/s12974-018-1376-1

Jayadevappa, R., Chhatre, S., Malkowicz, S. B., Parikh, R. B., Guzzo, T., and Wein, A. J. (2019). Association between Androgen Deprivation Therapy Use and Diagnosis of Dementia in Men with Prostate Cancer. *JAMA Netw. Open* 2, e196562. doi:10.1001/jamanetworkopen.2019.6562

Kaneko, N., Kurata, M., Yamamoto, T., Morikawa, S., and Masumoto, J. (2019). The Role of Interleukin-1 in General Pathology. *Inflamm. Regener* 39, 12. doi:10.1186/s41232-019-0101-5

Kasuga, K., Shimohata, T., Nishimura, A., Shiga, A., Mizuguchi, T., Tokunaga, J., et al. (2009). Identification of Independent APP Locus Duplication in Japanese Patients with Early-Onset Alzheimer Disease. *J. Neurol. Neurosurg. Psychiatry* 80, 1050–1052. doi:10.1136/jnnp.2008.161703

Ke, Y., Dramiga, J., Schütz, U., Kril, J. J., Ittner, L. M., Schröder, H., et al. (2012). Tau-mediated Nuclear Depletion and Cytoplasmic Accumulation of SFPQ in Alzheimer's and Pick's Disease. *PLoS One* 7, e35678. doi:10.1371/journal.pone.0035678

Kim, V. N., Han, J., and Siomi, M. C. (2009). Biogenesis of Small RNAs in Animals. *Nat. Rev. Mol. Cel. Biol.* 10, 126–139. doi:10.1038/nrm2632

Kirova, A.-M., Bays, R. B., and Lagalwar, S. (2015). Working Memory and Executive Function Decline across normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *Biomed. Res. Int.* 2015, 1–9. doi:10.1155/2015/748212

Knott, G. J., Bond, C. S., and Fox, A. H. (2016). The DBHS Proteins SFPQ, NONO and PSPC1: a Multipurpose Molecular Scaffold. *Nucleic Acids Res.* 44, 3989–4004. doi:10.1093/nar/gkw271

Korbel, J. O., Tirosh-Wagner, T., Urban, A. E., Chen, X.-N., Kasowski, M., Dai, L., et al. (2009). The Genetic Architecture of Down Syndrome Phenotypes Revealed by High-Resolution Analysis of Human Segmental Trisomies. *Proc. Natl. Acad. Sci.* 106, 12031–12036. doi:10.1073/pnas.0813248106

Lahiri, D. K., and Ge, Y.-W. (2004). Role of the APP Promoter in Alzheimer's Disease: Cell Type-specific Expression of the β-Amyloid Precursor Protein. *Ann. N. Y. Acad. Sci.* 1030, 310–316. doi:10.1196/annals.1329.039

Lahiri, D. K., and Nall, C. (1995). Promoter Activity of the Gene Encoding the Beta-Amyloid Precursor Protein Is Up-Regulated by Growth Factors, Phorbol Ester, Retinoic Acid and Interleukin-1. *Mol. Brain Res.* 32, 233–240. doi:10.1016/0169-328x(95)00078-7

Lahiri, D. K., and Robakis, N. K. (1991). The Promoter Activity of the Gene Encoding Alzheimer β-amyloid Precursor Protein (APP) Is Regulated by Two Blocks of Upstream Sequences. *Mol. Brain Res.* 9, 253–257. doi:10.1016/0169-328x(91)90009-m

Liang, C., Zhu, H., Xu, Y., Huang, L., Ma, C., Deng, W., et al. (2012). MicroRNA-153 Negatively Regulates the Expression of Amyloid Precursor Protein and Amyloid Precursor-like Protein 2. *Brain Res.* 1455, 103–113. doi:10.1016/j.brainres.2011.10.051

Lim, Y. W., James, D., Huang, J., and Lee, M. (2020). The Emerging Role of the RNA-Binding Protein SFPQ in Neuronal Function and Neurodegeneration. *Int. J. Mol. Sci.* 21, 7151. doi:10.3390/ijms21197151

Liu, C.-G., Song, J., Zhang, Y.-Q., and Wang, P.-C. (2014b). MicroRNA-193b Is a Regulator of Amyloid Precursor Protein in the Blood and Cerebrospinal Fluid Derived Exosomal microRNA-193b Is a Biomarker of Alzheimer's Disease. *Mol. Med. Rep.* 10, 2395–2400. doi:10.3892/mmr.2014.2484

Liu, C.-g., Wang, J.-l., Li, L., Xue, L.-x., Zhang, Y.-q., and Wang, P.-c. (2014a). MicroRNA-135a and -200b, Potential Biomarkers for Alzheimer's Disease, Regulate β Secretase and Amyloid Precursor Protein. *Brain Res.* 1583, 55–64. doi:10.1016/j.brainres.2014.04.026

Liu, H. Y., Fu, X., Li, Y. F., Li, X. L., Ma, Z. Y., Zhang, Y., et al. (2019). miR-15b-5p Targeting Amyloid Precursor Protein Is Involved in the Anti-amyloid Eflect of Curcumin in swAPP695-Hek293 Cells. *Neural Regen. Res.* 14, 1603–1609. doi:10.4103/1673-5374.255979

Long, J. M., and Lahiri, D. K. (2011). MicroRNA-101 Downregulates Alzheimer's Amyloid-β Precursor Protein Levels in Human Cell Cultures and Is Differentially Expressed. *Biochem. Biophysical Res. Commun.* 404, 889–895. doi:10.1016/j.bbrc.2010.12.053

Long, J. M., Maloney, B., Rogers, J. T., and Lahiri, D. K. (2019). Novel Upregulation of Amyloid-β Precursor Protein (APP) by microRNA-346 via Targeting of APP mRNA 5′-untranslated Region: Implications in Alzheimer's Disease. *Mol. Psychiatry* 24, 345–363. doi:10.1038/s41380-018-0266-3

Long, J. M., Ray, B., and Lahiri, D. K. (2012). MicroRNA-153 Physiologically Inhibits Expression of Amyloid-β Precursor Protein in Cultured Human Fetal Brain Cells and Is Dysregulated in a Subset of Alzheimer Disease Patients. *J. Biol. Chem.* 287, 31298–31310. doi:10.1074/jbc.M112.366336

López-lastra, M., Rivas, A., and Barría, M. I. (2005). Protein Synthesis in Eukaryotes: the Growing Biological Relevance of Cap-independent Translation Initiation. *Biol. Res.* 38, 121–146. doi:10.4067/s0716-97602005000200003

Lott, I. T., and Head, E. (2019). Dementia in Down Syndrome: Unique Insights for Alzheimer Disease Research. *Nat. Rev. Neurol.* 15, 135–147. doi:10.1038/s41582-018-0132-6

Lu, J., Shu, R., and Zhu, Y. (2018). Dysregulation and Dislocation of SFPQ Disturbed DNA Organization in Alzheimer's Disease and Frontotemporal Dementia. *J. Alzheimers Dis.* 61, 1311–1321. doi:10.3233/JAD-170659

Mucke, L., and Selkoe, D. J. (2012). Neurotoxicity of Amyloid -Protein: Synaptic and Network Dysfunction. *Cold Spring Harbor Perspect. Med.* 2, a006338. doi:10.1101/cshperspect.a006338

Nadal, M., Prekovic, S., Gallastegui, N., Helsen, C., Abella, M., Zielinska, K., et al. (2017). Structure of the Homodimeric Androgen Receptor Ligand-Binding Domain. *Nat. Commun.* 8, 14388. doi:10.1038/ncomms14388

Nakagawa, S., Yamazaki, T., and Hirose, T. (2018). Molecular Dissection of Nuclear Paraspeckles: towards Understanding the Emerging World of the RNP Milieu. *Open Biol.* 8, 180150. doi:10.1098/rsob.180150

Napoli, I., Mercaldo, V., Boyl, P. P., Eleuteri, B., Zalfa, F., De Rubeis, S., et al. (2008). The Fragile X Syndrome Protein Represses Activity-dependent Translation through CYFIP1, a New 4E-BP. *Cell* 134, 1042–1054. doi:10.1016/j.cell.2008.07.031

Nevedomskaya, E., Stelloo, S., van der Poel, H. G., de Jong, J., Wessels, L. F. A., Bergman, A. M., et al. (2016). Androgen Receptor DNA Binding and Chromatin Accessibility Profiling in Prostate Cancer. *Genomics Data* 7, 124–126. doi:10.1016/j.gdata.2015.12.020

Nguyen, K. V. (2019). β-Amyloid Precursor Protein (APP) and the Human Diseases. *AIMS Neurosci.* 6, 273–281. doi:10.3934/Neuroscience.2019.4.273

O'Donnell, W. T., and Warren, S. T. (2002). A Decade of Molecular Studies of Fragile X Syndrome. *Annu. Rev. Neurosci.* 25, 315–338. doi:10.1146/annurev.neuro.25.112701.142909

Panza, F., Lozupone, M., Logroscino, G., and Imbimbo, B. P. (2019). A Critical Appraisal of Amyloid-β-Targeting Therapies for Alzheimer Disease. *Nat. Rev. Neurol.* 15, 73–88. doi:10.1038/s41582-018-0116-6

Pasciuto, E., Ahmed, T., Wahle, T., Gardoni, F., D'Andrea, L., Pacini, L., et al. (2015). Dysregulated ADAM10-Mediated Processing of APP during a Critical Time Window Leads to Synaptic Deficits in Fragile X Syndrome. *Neuron* 87, 382–398. doi:10.1016/j.neuron.2015.06.032

Patel, A., Lee, H. O., Jawerth, L., Maharana, S., Jahnel, M., Hein, M. Y., et al. (2015). A Liquid-To-Solid Phase Transition of the ALS Protein FUS Accelerated by Disease Mutation. *Cell* 162, 1066–1077. doi:10.1016/j.cell.2015.07.047

Patel, N., Hoang, D., Miller, N., Ansaloni, S., Huang, Q., Rogers, J. T., et al. (2008). MicroRNAs Can Regulate Human APP Levels. *Mol. Neurodegeneration* 3, 10. doi:10.1186/1750-1326-3-10

Piñol-Roma, S., and Dreyfuss, G. (1993). hnRNP proteins:Localization and Transport between the Nucleus and the Cytoplasm. *Trends Cel Biol.* 3, 151–155. doi:10.1016/0962-8924(93)90135-n

Pollwein, P. (1993). Overlapping Binding Sites of Two Different Transcription Factors in the Promoter of the Human Gene for the Alzheimer Amyloid Precursor Protein. *Biochem. Biophys. Res. Commun.* 190, 637–647. doi:10.1006/bbrc.1993.1096

Prasher, V. P., Farrer, M. J., Kessling, A. M., Fisher, E. M. C., West, R. J., Barber, P. C., et al. (1998). Molecular Mapping of Alzheimer-type Dementia in Down's Syndrome. *Ann. Neurol.* 43, 380–383. doi:10.1002/ana.410430316

Quitschke, W. W., and Goldgaber, D. (1992). The Amyloid Beta-Protein Precursor Promoter. A Region Essential for Transcriptional Activity Contains a Nuclear Factor Binding Domain. *J. Biol. Chem.* 267, 17362–17368. doi:10.1016/s0021-9258(18)41934-5

Quitschke, W. W., Taheny, M. J., Fochtmann, L. J., and Vostrov, A. A. (2000). Differential Effect of Zinc finger Deletions on the Binding of CTCF to the Promoter of the Amyloid Precursor Protein Gene. *Nucleic Acids Res.* 28, 3370–3378. doi:10.1093/nar/28.17.3370

Quitschke, W. W. (1994). Two Nuclear Factor Binding Domains Activate Expression from the Human Amyloid Beta-Protein Precursor Promoter. *J. Biol. Chem.* 269, 21229–21233. doi:10.1016/s0021-9258(17)31952-x

Rajagopalan, L. E., Westmark, C. J., Jarzembowski, J. A., and Malter, J. S. (1998). hnRNP C Increases Amyloid Precursor Protein (APP) Production by Stabilizing APP mRNA. *Nucleic Acids Res.* 26, 3418–3423. doi:10.1093/nar/26.14.3418

Rogers, J. T., Bush, A. I., Cho, H.-H., Smith, D. H., Thomson, A. M., Friedlich, A. L., et al. (2008). Iron and the Translation of the Amyloid Precursor Protein (APP) and Ferritin mRNAs: Riboregulation against Neural Oxidative Damage in Alzheimer's Disease. *Biochem. Soc. Trans.* 36, 1282–1287. doi:10.1042/BST0361282

Rogers, J. T., Leiter, L. M., McPhee, J., Cahill, C. M., Zhan, S.-S., Potter, H., et al. (1999). Translation of the Alzheimer Amyloid Precursor Protein mRNA Is Up-Regulated by Interleukin-1 through 5′-Untranslated Region Sequences. *J. Biol. Chem.* 274, 6421–6431. doi:10.1074/jbc.274.10.6421

Rogers, J. T., Randall, J. D., Cahill, C. M., Eder, P. S., Huang, X., Gunshin, H., et al. (2002). An Iron-Responsive Element Type II in the 5′-Untranslated Region of the Alzheimer's Amyloid Precursor Protein Transcript. *J. Biol. Chem.* 277, 45518–45528. doi:10.1074/jbc.M207435200

Rosario, E. R., Chang, L., Head, E. H., Stanczyk, F. Z., and Pike, C. J. (2011). Brain Levels of Sex Steroid Hormones in Men and Women during normal Aging and in Alzheimer's Disease. *Neurobiol. Aging* 32, 604–613. doi:10.1016/j.neurobiolaging.2009.04.008

Rovelet-Lecrux, A., Hannequin, D., Raux, G., Meur, N. L., Laquerrière, A., Vital, A., et al. (2006). APP Locus Duplication Causes Autosomal Dominant Early-Onset Alzheimer Disease with Cerebral Amyloid Angiopathy. *Nat. Genet.* 38, 24–26. doi:10.1038/ng1718

Ruberti, F., Barbato, C., and Cogoni, C. (2010). Post-transcriptional Regulation of Amyloid Precursor Protein by microRNAs and RNA Binding Proteins. *Commun. Integr. Biol.* 3, 499–503. doi:10.4161/cib.3.6.13172

Shaftel, S. S., Griffin, W. S. T., and O'Banion, M. K. (2008). The Role of Interleukin-1 in Neuroinflammation and Alzheimer Disease: an Evolving Perspective. *J. Neuroinflammation* 5, 7. doi:10.1186/1742-2094-5-7

Shaulian, E., and Karin, M. (2002). AP-1 as a Regulator of Cell Life and Death. *Nat. Cel Biol.* 4, E131–E136. doi:10.1038/ncb0502-e131

Sleegers, K., Brouwers, N., Gijselinck, I., Theuns, J., Goossens, D., Wauters, J., et al. (2006). APP Duplication Is Sufficient to Cause Early Onset Alzheimer's Dementia with Cerebral Amyloid Angiopathy. *Brain* 129, 2977–2983. doi:10.1093/brain/awl203

Smale, S. T., and Kadonaga, J. T. (2003). The RNA Polymerase II Core Promoter. *Annu. Rev. Biochem.* 72, 449–479. doi:10.1146/annurev.biochem.72.121801.161520

Stelloo, S., Bergman, A. M., and Zwart, W. (2019). Androgen Receptor Enhancer Usage and the Chromatin Regulatory Landscape in Human Prostate Cancers. *Endocr. Relat. Cancer* 26, R267–R285. doi:10.1530/ERC-19-0032

Strittmatter, W. J., Weisgraber, K. H., Huang, D. Y., Dong, L. M., Salvesen, G. S., Pericak-Vance, M., et al. (1993). Binding of Human Apolipoprotein E to Synthetic Amyloid Beta Peptide: Isoform-specific Effects and Implications for Late-Onset Alzheimer Disease. *Proc. Natl. Acad. Sci.* 90, 8098–8102. doi:10.1073/pnas.90.17.8098

Swaminathan, S., Huentelman, M. J., Corneveaux, J. J., Myers, A. J., Faber, K. M., Foroud, T., et al. (2012). Analysis of Copy Number Variation in Alzheimer's Disease in a Cohort of Clinically Characterized and Neuropathologically Verified Individuals. *PLoS One* 7, e50640. doi:10.1371/journal.pone.0050640

Takayama, K.-i., and Inoue, S. (2013). Transcriptional Network of Androgen Receptor in Prostate Cancer Progression. *Int. J. Urol.* 20, 756–768. doi:10.1111/iju.12146

Takayama, K.-i., Tsutsumi, S., Suzuki, T., Horie-Inoue, K., Ikeda, K., Kaneshiro, K., et al. (2009). Amyloid Precursor Protein Is a Primary Androgen Target Gene that Promotes Prostate Cancer Growth. *Cancer Res.* 69, 137–142. doi:10.1158/0008-5472.CAN-08-3633

Takayama, K. I., Fujiwara, K., and Inoue, S. (2019). Amyloid Precursor Protein, an Androgen-regulated Gene, Is Targeted by RNA-binding Protein PSF/SFPQ in Neuronal Cells. *Genes Cells* 24, 719–730. doi:10.1111/gtc.12721

Tewari, A. K., Yardimci, G., Shibata, Y., Sheffield, N. C., Song, L., Taylor, B. S., et al. (2012). Chromatin Accessibility Reveals Insights into Androgen Receptor Activation and Transcriptional Specificity. *Genome Biol.* 13, R88. doi:10.1186/gb-2012-13-10-r88

Thonberg, H., Fallström, M., Björkström, J., Schoumans, J., Nennesmo, I., and Graff, C. (2011). Mutation Screening of Patients with Alzheimer Disease Identifies APP Locus Duplication in a Swedish Patient. *BMC Res. Notes* 4, 476. doi:10.1186/1756-0500-4-476

Trejo, J., Massamiri, T., Deng, T., Dewji, N. N., Bayney, R. M., and Brown, J. H. (1994). A Direct Role for Protein Kinase C and the Transcription Factor Jun/AP-1 in the Regulation of the Alzheimer's Beta-Amyloid Precursor Protein Gene. *J. Biol. Chem.* 269, 21682–21690. doi:10.1016/s0021-9258(17)31860-4

Vilardo, E., Barbato, C., Ciotti, M., Cogoni, C., and Ruberti, F. (2010). MicroRNA-101 Regulates Amyloid Precursor Protein Expression in Hippocampal Neurons. *J. Biol. Chem.* 285, 18344–18351. doi:10.1074/jbc.M110.112664

Vogrinc, D., Goričar, K., and Dolžan, V. (2021). Genetic Variability in Molecular Pathways Implicated in Alzheimer's Disease: A Comprehensive Review. *Front. Aging Neurosci.* 13, 646901. doi:10.3389/fnagi.2021.646901

Vostrov, A. A., Quitschke, W. W., Vidal, F., Schwarzman, A. L., and Goldaber, D. (1995). USF Binds to the APBα Sequence in the Promoter of the Amyloid β-protein Precursor Gene. *Nucl. Acids Res.* 23, 2734–2741. doi:10.1093/nar/23.14.2734

Vostrov, A. A., Taheny, M. J., Izkhakov, N., and Quitschke, W. W. (2010). A Nuclear Factor-Binding Domain in the 5'-untranslated Region of the Amyloid Precursor Protein Promoter: Implications for the Regulation of Gene Expression. *BMC Res. Notes* 3, 4. doi:10.1186/1756-0500-3-4

Wahjoepramono, E. J., Wijaya, L. K., Taddei, K., Martins, G., Howard, M., de Ruyck, K., et al. (2008). Distinct Effects of Testosterone on Plasma and Cerebrospinal Fluid Amyloid-β Levels. *J. Alzheimers Dis.* 15, 129–137. doi:10.3233/jad-2008-15111

Wang, H., and Eckel, R. H. (2014). What Are Lipoproteins Doing in the Brain?. *Trends Endocrinol. Metab.* 25, 8–14. doi:10.1016/j.tem.2013.10.003

Westmark, C. J., and Malter, J. S. (2007). FMRP Mediates mGluR5-dependent Translation of Amyloid Precursor Protein. *Plos Biol.* 5, e52. doi:10.1371/journal.pbio.0050052

Westmark, C. J., and Malter, J. S. (2012). The Regulation of AβPP Expression by RNA-Binding Proteins. *Ageing Res. Rev.* 11, 450–459. doi:10.1016/j.arr.2012.03.005

Westmark, C. J., Westmark, P. R., O'Riordan, K. J., Ray, B. C., Hervey, C. M., Salamat, M. S., et al. (2011). Reversal of Fragile X Phenotypes by Manipulation

of AβPP/Aβ Levels in Fmr1KO Mice. *PLoS One* 6, e26549. doi:10.1371/journal.pone.0026549

Wiseman, F. K., Al-Janabi, T., Hardy, J., Karmiloff-Smith, A., Nizetic, D., Tybulewicz, V. L. J., et al. (2015). A Genetic Cause of Alzheimer Disease: Mechanistic Insights from Down Syndrome. *Nat. Rev. Neurosci.* 16, 564–574. doi:10.1038/nrn3983

Wolozin, B., and Ivanov, P. (2019). Stress Granules and Neurodegeneration. *Nat. Rev. Neurosci.* 20, 649–666. doi:10.1038/s41583-019-0222-5

Xiong, M., Jiang, H., Serrano, J. R., Gonzales, E. R., Wang, C., Gratuze, M., et al. (2021). APOE Immunotherapy Reduces Cerebral Amyloid Angiopathy and Amyloid Plaques while Improving Cerebrovascular Function. *Sci. Transl. Med.* 13, eabd7522. doi:10.1126/scitranslmed.abd7522

Yang, Y., Quitschke, W., Vostrov, A. A., and Brewer, G. J. (1999). CTCF Is Essential for Up-Regulating Expression from the Amyloid Precursor Protein Promoter during Differentiation of Primary Hippocampal Neurons. *J. Neurochem.* 73, 2286–2298. doi:10.1046/j.1471-4159.1999.0732286.x

Yeh, S. H., Yang, W. B., Gean, P. W., Hsu, C. Y., Tseng, J. T., Su, T. P., et al. (2011). Translational and Transcriptional Control of Sp1 against Ischaemia through a Hydrogen Peroxide-Activated Internal Ribosomal Entry Site Pathway. *Nucleic Acids Res.* 39, 5412–5423. doi:10.1093/nar/gkr161

Younas, N., Zafar, S., Shafiq, M., Noor, A., Siegert, A., Arora, A. S., et al. (2020). SFPQ and Tau: Critical Factors Contributing to Rapid Progression of Alzheimer's Disease. *Acta Neuropathol.* 140, 317–339. doi:10.1007/s00401-020-02178-y

Zhang, B., Chen, C. F., Wang, A. H., and Lin, Q. F. (2015). MiR-16 Regulates Cell Death in Alzheimer's Disease by Targeting Amyloid Precursor Protein. *Eur. Rev. Med. Pharmacol. Sci.* 19, 4020–4027.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.