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The CircRNAs for Diagnostic, Prognostic, and Therapy in Alzheimer's Disease

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Abstract

The structure and biological function of circular RNAs (circRNAs) in regulating gene expression in a cell is far from known. CircRNAs are unique molecules that contain potent regulatory elements. CircRNAs actively interact with miRNAs (sponging), affecting their regulation and functions. In addition, circRNAs have roles in transcriptional regulation, splicing, and peptide synthesis. With all these properties, circRNAs could play an essential role in diseases, especially Alzheimer's. Their role in early diagnosis, previous to present symptoms, prognosis associated with neuropathological AD of specific circRNAs, and one of their primary functions is to act as a sponge for miRNAs, which could be a starting point for future gene therapy. This review aims to summarize the current knowledge of these exciting molecules and their potential use as new markers for AD risk. This article will focus on circRNAs deregulated in Alzheimer's.

Keywords

CircRNA, Alzheimer's Disease, miRNAs, Diagnosis, Therapy, Dementia

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia with no cure and affects over 50 million people worldwide [1] [2]. It affects 10% - 30% of the population older than 65 [3] [4], and about 1% - 5% of the cases have genetic causes and the symptoms present in the population younger than 65 years old [5]. The disease has a progressing neurodegenerative process associated with undetectable intraneural lesions [6] [7], occurring before cognitive symptoms [8]. After several decades, the patients show mild memory loss that gradually becomes a severe impairment of executive and cognitive functions [9].

The major histopathological hallmarks of AD are senile plaques characterized by the accumulation of amyloid β (Aβ) peptides, resulting from cleavage of the transmembrane protein APP (amyloid precursor protein) and neurofibrillary tangles (NFTs), constituted of highly phosphorylated microtubule-associated protein Tau (MAPT), mainly present in the cytoplasm of neuronal axons, pre- and post-synaptic regions and the cerebrospinal fluid (CSF), both aggregates are founded in the neocortex, hippocampus, and other subcortical brain regions [10].

It has been difficult to explain how AD pathology arises. The general hypothesis suggests that forming amyloid plaques leads to neuronal degeneration and death in AD patients [11]. However, this amyloid hypothesis cannot explain the onset and progression of AD. Recently, new information on the role of RNA has significantly impacted neurodegenerative diseases.

This review will summarize the current evidence showing how circRNAs expression and function affect the biogenesis, expression, processing, and localization of coding and noncoding RNAs (ncRNAs), highlighting the great potential as diagnostic and prognostic biomarkers conferred by the characteristics of circRNAs that have covalently closed ends that endow them with excellent stability in blood and other body fluids. Besides, circRNAs could be considered therapeutic agents by regulating the expression of miRNAs that regulate genes, directly the genes (transcriptional factor) or proteins (template to translate) involved in the pathophysiology of AD.

2. CircRNA

First discovered in viruses, circRNAs have been reported in several species. Until 2017, circRNAs were recognized as not noncoding RNAs [12], capable of regulating gene expression through different mechanisms: working as miRNA sponging, interactions with RNA-binding proteins (RBPs), working as template protein and participating in the transcriptional complex it depended on its nature, it has been argued that circRNAs are a by-product of splicing and may originate from introns, exons, or both [12] [13]. The expression pattern of circRNAs is highly conserved. 80% of all efficiently expressed mouse neuronal circRNAs are also detected in the human brain [14]. These particular types of RNA are represented in physiological and pathological states. There are multiple studies related to diverse human diseases like neurological and neurodegenerative diseases [15] [16] [17] [18], cancer [18] [19] [20] [21], immune response [22], and many other diseases.

3. Backsplicing Mechanisms and CircRNA Biogenesis

Backsplicing is the fundamental component of circRNA molecule synthesis [16] [23]. It consists of the direct ligation of the exonic downstream 5' donor site with the upstream 3' acceptor site, which results in the circularization of the RNA molecule and the absence of the two existing extremities at their linear counterparts [24]-[29]. circRNAs are single-stranded RNA molecules presenting a

circular conformation catalyzed by RBPs [16] [24] [30]. These circular structures are derived from pre-mRNA, transcribed by RNA-polymerase II, and then processed by the spliceosome machinery [17] [26] [31] [32] [33] [34]. CircRNA is more resistant to exonuclease than the linear transcript and is, therefore, more stable in cells [35] [36], and inhibits the function of miRNA by acting as miRNA sponges [37]. CircRNAs are small molecules, conserved, and able to regulate 30% of protein-coding genes through multiple miRNA binding sites in their conformation, allowing them to capture numerous miRNAs and indirectly control gene expression [38]. The backsplicing mechanism to produce distinct types of circRNAs can be induced by cis-elements (noncoding binding regions capable of regulating transcription), promoting a viable source of "exon shuffling", resulting in alternative splicing [29]. Backsplicing is highly dependent on complementary sequences present in the flanking introns that are present in the circRNA and are exceptionally long [39]. The RBPs may serve as regulatory factors in the formation of circRNA molecules. miRNAs are short noncoding RNAs (21 - 24 nt) implicated in many cellular processes, including proliferation, differentiation, senescence, stress response, and apoptosis [4] [16] (**Figure 1**).

4. CircRNA Expression

Although circRNAs can be found in various organ systems such as the brain, heart, kidney, skin, lung, liver, and blood, they are highly abundant in the central

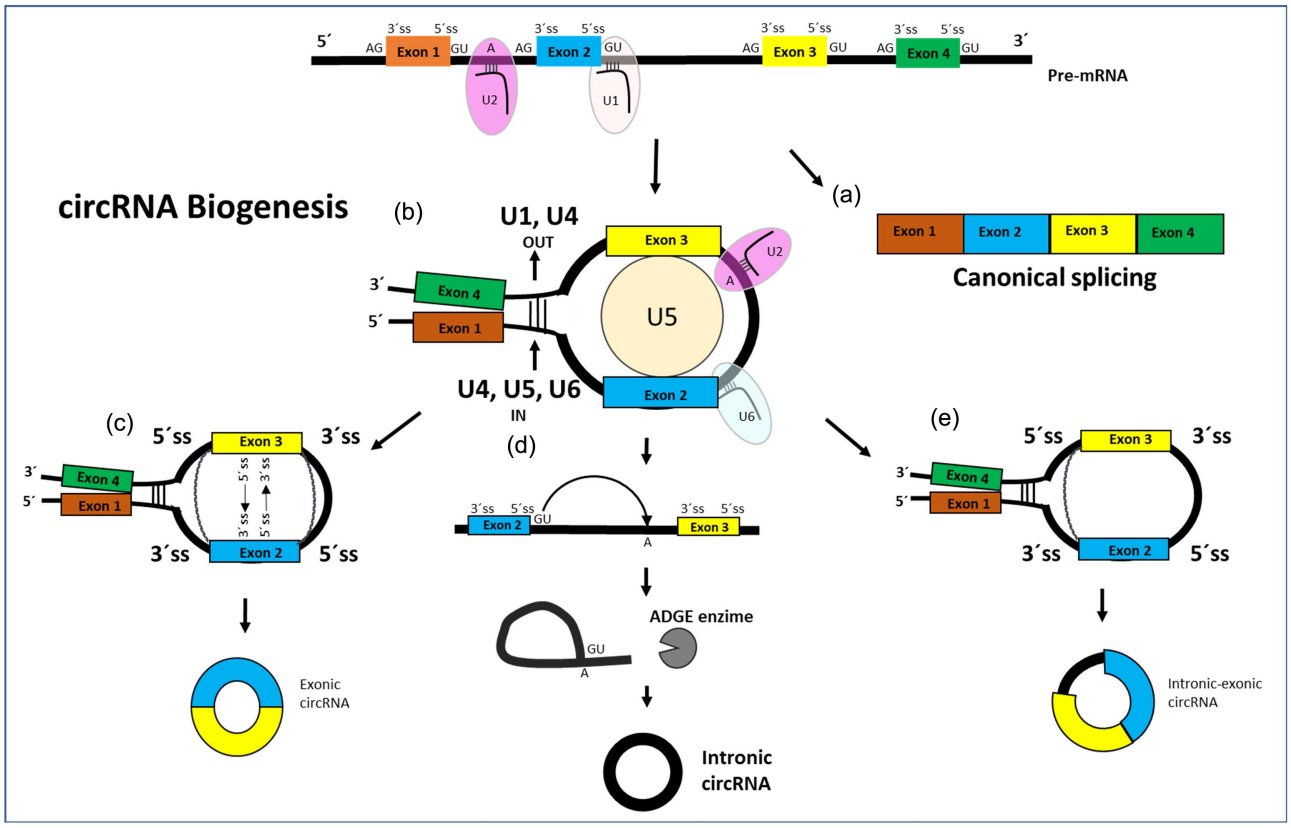

Figure 1. circRNA Biogenesis.

nervous system (CNS) [4] [40] [41]. Several reasons could explain this phenomenon: 1) The levels of RBPs or splicing factors in the CNS are higher and may function as trans-acting factors to induce circRNA formation [42]. 2) The brain contains an abundance of neuronal genes that play roles in neurogenesis, neurodevelopment, and neuronal differentiation [4] [27]. 3) Neuronal genes typically contain long (>10 kb) introns, facilitating the formation of circRNA [43]. 4) circRNAs show a relatively longer half-life than linear RNA [44]. The average half-life of circRNAs is higher than the corresponding linear isoforms [45]. In addition, 5) neurons had a slow division rate, and circRNAs may accumulate more in the brain than in other tissues [14] [46]. CircRNA levels are dynamically modulated in neurons, both during differentiation and following bursts of electrical activity, and accumulate with age, and many of them are enriched in synapses. The available data suggest that circRNAs have essential roles in synaptic plasticity and neuronal function [14]. Altered circRNAs in several neurodegenerative diseases are the primary RNA isoforms derived from some neuronal genes [47], particularly CDR1as/ciRS-7 [14] [48]. Interestingly, circRNAs are enriched in the brain and build up during aging and age-related diseases. These extraordinary peculiarities make circRNAs potentially suitable as promising molecular biomarkers, especially for aging and neurodegenerative diseases [49]. In addition, a recent study reported that exosomal circRNAs could cross the blood-brain barrier (BBB), making them perfect candidates as potential diagnostic tools for neurodegenerative disease [50] [51].

5. Omics Approaches in CircRNA of Alzheimer's Disease

Bioinformatics is a powerful tool to identify miRNAs potentially regulated by AD-associated circRNAs and to predict miRNA-binding sites in circRNA sequences. It has been reported that over 70 miR-7 predicted binding sites were found in the circCDR1-AS sequence, and binding sites for several intriguing miRNAs in the other AD-associated circRNAs were also predicted. circHOMER1 contained five potential binding sites for miR-651, a miRNA predicted to target the AD-related genes Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2). Finally, circCORO1C, identified as coexpressing with the AD-related genes APP and SNCA, contains two predicted binding sites for miR-105, a miRNA predicted to target APP and SNCA42, and circCORO1C could have good potential to be counted as novel markers of AD risk and diagnosis and highly associated with neuropathological AD status vs. controls and other AD severity [52]. The validation using a quantitative polymerase chain reaction approach showed changes in the expression of 8 circRNAs (circHOMER1, circDOCK1, circFMN1, circKCNN2, circRTN4, circMAN2A1, circMAP7, and circPICALM). Average expression changes between patients with AD and controls followed the exact directions. They confirmed an exacerbated alteration in circRNA expression in the autosomal dominant AD (ADAD) group compared with sporadic AD. Two circRNAs (circHOMER1 and circKCNN2) also showed significant expression

alterations in the group of frontotemporal lobar degeneration with Tau pathology (FTLD-tau) and TLD-TDP43 (TAR DNA-binding protein 43 (TDP-43)), a major pathological protein of sporadic and familial frontotemporal lobar degeneration, respectively [53]. A study with a 7-month-old senescence-accelerated mouse prone 8 (SAMP8) model brain through deep RNA sequencing showed 235 significantly dysregulated circRNA transcripts, 30 significantly dysregulated miRNAs, and 1202 significantly dysregulated mRNAs and constructed networks with Go analysis. The results show the regulation of the development of AD from various angles, for instance, axon terminus, synapse, and involvement in the regulation of Aβ clearance (Hmgb2) and myelin function (Dio2) [37]. Li *et al.* 2020 [54] proposed that circ-AXL, circ-GPHN, and circ-PCCA hold clinical implications in AD patients. A circRNA expression profile via microarray revealed that 112 circRNAs were upregulated and 51 circRNAs were downregulated in AD patients compared with control subjects. These circRNAs were enriched in AD-related pathways such as the neurotrophin signaling pathway, the Natural Killer (NK) cell-mediated cytotoxicity, and cholinergic synapse. In AD patients, circ-AXL and circ-GPHN negatively correlate with the mini-mental state examination score, while circ-PCCA and circ-HAUS4 correlate positively; circ-AXL negatively correlated with Aβ42, while circ-PCCA, circ-HAUS4, and circ-KIF18B correlated positively; circ-AXL and circ-GPHN positively correlated with truncated Tau (t-Tau), whereas circ-HAUS4 correlated negatively; circ-AXL positively correlated with phosphorylated Tau (p-Tau), and it has been identified that circ-AXL, circ-GPHN, and circ-PCCA hold clinical implications for guiding disease management in AD patients [54]. **Table 1** shows a list of CircRNA associated with Alzheimer's disease.

Glial neuroinflammation plays a pivotal role in AD progression, contributing to neuronal injury [55]. Li *et al.* 2020 [54] obtained a circRNA expression profile with disease and risk progression from the CSF samples of AD and controls and discovered that circLPAR1, circAXL, and circGPHN could predict higher AD risk, whereas circPCCA, circHAUS4, circKIF18B, and circTTC39C could predict lower AD risk. These circRNAs can modulate the transcription of their originating genes negatively or positively, such as AXL receptor tyrosine kinase (AXL) or Tetratricopeptide Repeat Domain 39C (TTC39C), and increase AD susceptibility by dysregulating neuroinflammation and neuronal cell apoptosis. Besides, they are involved in AD pathogenesis, reducing the AD severity with its overexpression by sponging mir-138-5p and inhibiting Tau phosphorylation, a histopathological hallmark of AD [54]. The results of circRNAs from next-generation RNA sequencing data of Ma *et al.* 2019 [56] suggest that circTRPC6 and circNME7 might be a biomarker for the early diagnosis of AD because they are involved in Aβ production and cognitive performance (circTRPC6) and neuronal differentiation and development (circNME7) [56]. Transient receptor potential canonical 6 (TRPC6), which specifically interacts with APP leading to inhibition of its cleavage by g-secretase and reduction in Aβ production [30]. Furthermore, TRPC6 mRNA levels in the blood cells are remarkably reduced in AD.

Table 1. CircRNA in Alzheimer's disease.

CircRNA	Sponge or mechanism of action	Possible pathogenic role or mechanism	Tissue or body fluid	Potential biomarker	References
ciRS-7/circCDR1as	miR-7	*β*-Amyloid deposition, degradation, reduce UBE2A and inhibits NF-kB signaling pathway, reduction UCHL1, APP, BACE1 generating accumulation A*β*.	Brain		[16] [18] [49] [64]-[69] [71] [72] [73] [97]
circHOMER1	miR-651	Postsynaptic regulation, as a miR-651 sponge, clinical severity, and Braak neuropathologic staging, AD diagnosis, target PSEN1, and PSEN2.	Brain entorhinal cortex	Yes	[52] [53] [76]
circCORO1C	miR-105	Coexpressed with APP and Sinuclein Alpha, target APP, SNCA.	Brain	Yes	[52] [79]
circHDAC9	miR-142-5p	Alleviated A*β*42-induced HN cell neurotoxicity via miR-142-5p.	Serum		[75]
	miR-138	Increase A*β* production, target Sirt1.	Serum		[85]
circ_0000950	miR-103	Enhance neuron apoptosis and promotes inflammatory response in AD through IL-2 and TNF-a.	Cellular AD model		[90]
circRTN4		Inhibits neuronal sprouting reduce A*β* deposition through BACE1.	Brain	Yes	[52] [53]
circDOCK1		Axonal outgrowth, spine morphogenesis, neuroinflammation, clinical severity, and Braak neuropathologic staging.	Brain, plasma	Yes	[52] [81]
circKIF1B		Axonal transport, vesicular traffic.	Brain, plasma	Yes	[81]
circA*β*-a		Translates into a novel A*β*175-containing A*β* polypeptide.	Brain, culture cell	Yes	[81] [84]
circDLG1		Axonal transport, vesicular traffic.	Brain, plasma	Yes	[81]
circLPAR1	Modulate transcription/ mir-212-3p	Neuroinflammation, neuronal cell apoptosis/oxidative stress target PPAR1, ZNF217.	CSF, blood	Yes	[54] [87]
circAXL	Modulate transcription	Neuroinflammation, and neuronal cell apoptosis, Predict higher AD risk target AXL.	CSF	Yes	[54]
circPCCA	mir-138-5p	Inhibits Tau phosphorylation, Predict lower AD risk.	CSF	Yes	[54]

Continued

circGPHN	Modulate transcription	Neuroinflammation, neuronal cell apoptosis, Predict higher AD risk, target GPHN.	CSF	Yes	[54]
circ_0131235		Target IGF2-receptor.	Brain	Yes	[98]
NF1-419		Neuroinflammation, reduction of inflammatory mediators (IL-6, IFN-β).	SAMP8 mice		[93]
circKCNN2		Clinical severity and Braak neuropathologic staging.	Brain		[53]
circPAR1		Predict higher AD risk.	CSF	Yes	[54]
circHAUS4		Predict lower AD risk.	CSF	Yes	[54]
circKIF18B		Predict lower AD risk.	CSF	Yes	[54]
circTTC39C		Predict lower AD risk.	CSF	Yes	[54]
circTRPC6		Regulate cognitive performance, reduction in Aβ production, Interacts with APP leading to inhibition of its cleavage by g-secretase, Early diagnosis.		Yes	[30] [56]
circNME7		Regulate neuronal differentiation and development, Early diagnosis.		Yes	[56]
circAPOE			Brain		[54]
circMAN2A1		Clinical severity and Braak neuropathologic staging.	Brain		[53] [58]
circFMN1		Clinical severity and Braak neuropathologic staging.	Brain		[53] [58]
circMAP7		Clinical severity and Braak neuropathologic staging.	Brain		[53] [58]
circTTLL7		Clinical severity and Braak neuropathologic staging.	Brain		[53] [58]
circPICALM		Clinical severity and Braak neuropathologic staging.	Brain		[53] [58]
circKIAA1586	hsa-miR-29b, hsa-miR-15a, hsa-miR-101			Yes	[61]
circ_0007556		Encoding the new Aβ-175 polypeptide variant called circAβ-a.			[84]
circCwc27		Pur-α overexpression largely phenocopied circCwc27 Knockdown in preventing Aβ deposition and cognitive decline.			[86]
mmu_circRNA_017963		Associated with different autophagosome and vesicular transport pathways.			[91]

Continued

circNF1-419		Thus, circNF1-419 increased autophagy, reducing the expression of Tau, p-Tau, Aβ1-42, and APOE, and ameliorated senile dementia by binding Dynamin-1 and AP2B1, influencing synapse in SAMP8 mice.	SAMP8 mice	[93]
hsa_circ_0003391	miR-574-5p	Downregulated in the peripheral blood of AD patients.	Blood	[95]
circPSEN1		ADAD is more severe in magnitude than AD.	Brain	[52]
mm10_circ_0027491	mmu-miR-122-5p	Myelin function.	SAMP8 mice cerebral cortex	[37]
mm10_circ_0027470		Aβ clearance, target mmu-let-7g-3p, Hmgb2.	SAMP8 mice cerebral cortex	[37]

patients [57]. One study compared circRNA expression measured by RNASeq in cerebral cortices of people with AD versus healthy control subjects (n = 291).

The circRNA for APOE (circAPOE) is more highly expressed in frontal lobe samples with AD than in control samples, but the effect size is comparable with its full-length linear mRNA counterpart [17]. After examining the correlation of each circRNA with three traits (AD versus control, clinical severity, and Braak neuropathologic staging), nine circRNAs passed the stringent test: circHOMER1, circDOCK1, circKCNN2, circMAN2A1, circFMN1, circRTN4, circMAP7, circTTLL7, and circPICALM. Another study examined eight of the nine circRNAs identified by Maurano *et al.* 2012 [58] using qPCR in frontal cortices from 19 sporadic AD, nine autosomal dominant AD, and 15 control brains [59], replicating the results of [58] [60].

Finally, a meta-analysis from multiple-microarray showed consistent differentially expressed genes (CDEGs) and differentially expressed miRNAs (DEmiRs). The circRNA-associated competing endogenous RNA network (cirCeNET) was constructed based on the competing endogenous RNA "(ceRNA) hypothesis". A total of 1872 CDEGs and 48 DEmiRs were screened across different datasets. By mapping CDEGs and DEmiRs into the cirCeNET, an AD-related circRNA-associated ceRNA network (ADcirCeNET) was constructed, including 3907 edges and 1407 nodes (276 circRNAs, 14 miRNAs, and 1117 mRNAs). It is worth mentioning the circRNA KIAA1586 was AD risk circRNA-associated ceRNAs and functions as a ceRNA that operates by competitively binding hsa-miR-29b, hsa-miR-15a, and hsa-miR-101 AD-risk miRNAs. The circRNA KIAA1586 may be a key risk factor in AD pathogenesis [61].

6. CircRNA in Alzheimer's Disease

The roles of circRNAs in AD are the most studied in neurodegenerative diseases

and have revealed a potential link between AD and circRNA; most studies have focused on AD. Age is a significant risk factor for neurodegeneration. Interestingly, age-related changes in alternative splicing patterns found in cognitively healthy adults are also observed in 95% of individuals with frontotemporal lobe dementia or AD patients, irrespective of age [62] [63].

In the brain tissue of AD patients, it has been demonstrated that ciRS-7 levels were significantly reduced in AD hippocampal CA1 samples versus age-matched healthy controls, which mediated sponge effect in miRNA-7, which can increase miRNA-7 in the neocortex and hippocampus. This increase in miRNA-7 appears to drive the selective down-regulation in the expression of the ubiquitin-conjugating enzyme E2A (UBE2A) [18] [49] [64]-[69]. UBE2A is an autophagic phagocytic protein, and it is essential for the brain in the clearance of amyloid peptides and other cytotoxic-related molecules produced by progressive degenerations of the human central nervous system [70] **Figure 2**.

Through the nuclear factor-kB (NF-kB) cytosol localization, ciRS-7 inhibits NF-KB translation and induces its localization to the cytoplasm. They are repressing the expression of ubiquitin C-Terminal Hydrolase L1 (UCHL1), which promotes the degradation of the cleavage of APP and b-site APP-cleaving enzyme 1 (BACE1), which has a significant function in the generation of amyloid β in AD [16] [18] [71] [72]. Lukiw *et al.* 2013 [66] reported that ciRS-7 acts as a competing endogenous miRNA sponge to inhibit miRNA-7 functions in the AD-affected brain. Furthermore, Zhao *et al.* 2016 [65] observed the network of

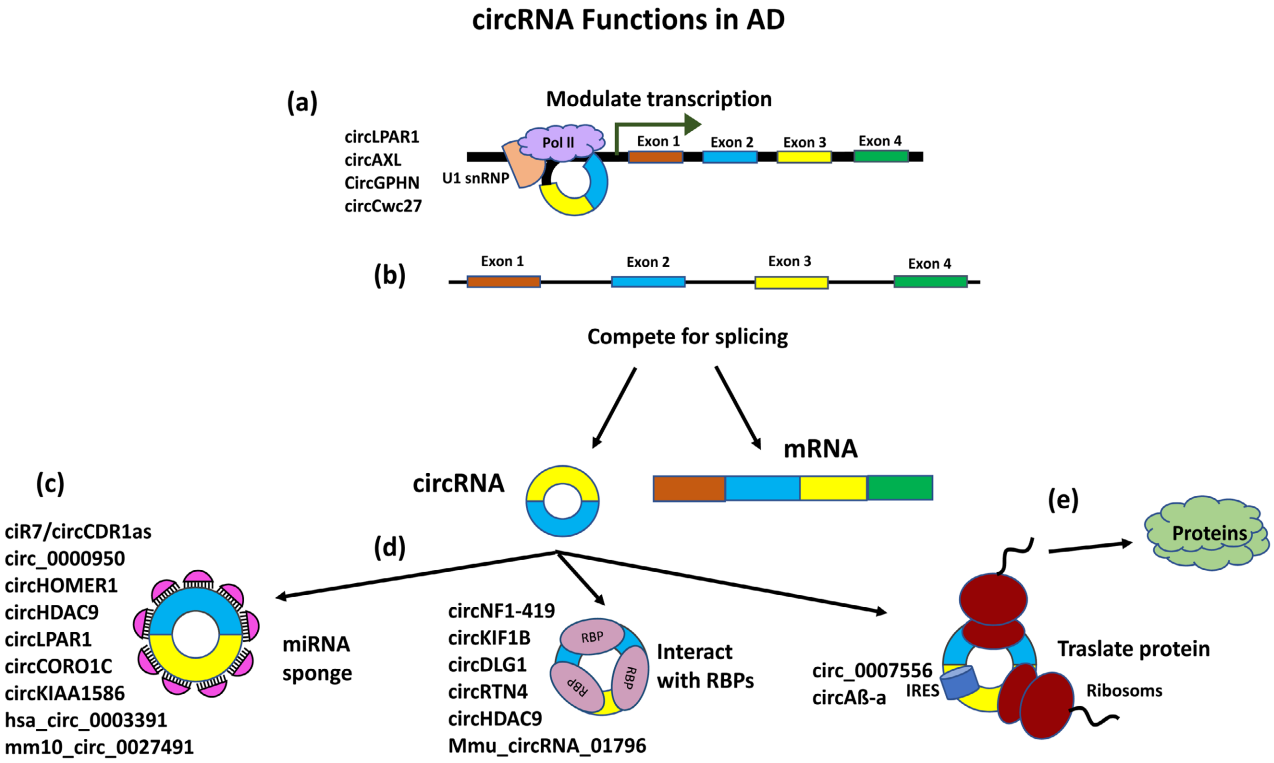

Figure 2. circRNA functions in AD.

ciRS-7-miRNA-7-UBE2A in sporadic AD neocortex and hippocampal CA1. On the other hand, synaptic dysfunction and abnormal processing of amyloid precursor protein are early pathological features in AD. Early pathological features in AD are synaptic dysfunction and abnormal processing of APP [65]. Interestingly, Shi *et al.* 2017 [73] proposed a neuroprotective role for the same circRNA by promoting APP and BACE1 protein degradation via the proteasome and lysosome pathways. All of this evidence testifies to a potential regulatory role for ciRS-7 in the etiology of AD [73]. Similarly, for circHDAC9, a neuroprotective role is reported. Besides, in Aβ42-treated HN cells, circHDAC9 overexpression can promote cell viability and repress cell apoptosis and inflammation via sponging miR-142-5p [74] [75].

The importance of circRNAs also lies in the genes from which they were spliced. The circRNA in the RTN4 gene inhibits neuronal sprouting and modulates AD by reducing the Aβ deposit through interaction with BACE1 and the circRNA in the Homer Scaffold Protein 1 (HOMER1) [52] [53] [76]. Both circRTN4 and circHOMER1 were significantly associated with AD diagnosis, clinical neurological staging, and dementia severity [52] [53]. In particular, circHOMER1 is very interesting considering that HOMER1 protein contributes to the postsynaptic density (PSD) by linking neural channels and receptors with which the Aβ protein in the AD brain can aberrantly combine [77] [78]. CircHOMER1 might be directly related to AD regulating PSEN1 and PSEN2 expression by binding its predicted sites for mir-651. Furthermore, circCORO1C co-expressed with APP and Sinuclein Alpha (SNCA) AD-related genes. This co-expression could be mediated through mir-105 and its predicted targets, the APP and SNCA genes [79].

The circRNA generated from the AD-associated gene Dedicator of Cytokinesis 1 (DOCK1) participated in axonal outgrowth, spine morphogenesis, and neuroinflammation and was identified as the best gene AD-related in astrocyte, language, and cognitive-specific modules of polygenic risk scores combined with brain expression profiles [52] [80]. Cochran's analysis demonstrated differential circRNA expression in blood isolating circKIF1B and circDLG1, whose genes are implicated in vesicular trafficking, to be good biomarker candidates because they appeared in both brain and plasma samples [81]. Remarkably, the most intriguing characteristic of some circRNAs is that, as already pointed out, when they contain exonic regions, they can be translated into peptides [82] [83]. In this respect, circ_0007556, encoding the new Aβ-175 polypeptide variant called circAβ-a, seems to represent the most direct connection between circRNAs and AD pathogenesis. This circRNA is generated from the circularization of some exons of the APP transcript. Has been detected circAβ-a in the brains of AD patients and controls and demonstrated, using *in vitro* models, that circAβ-a was efficiently translated into an Aβ-related protein (Aβ-175) and was further cleaved into Aβ-peptides, a hallmark of AD [84]. CDR1as/ciRS-7 is also strongly misregulated in the hippocampal CA1 region of AD patients [66]. The expression of miR-7 is significantly increased in the brains of sporadic AD patients,

which may be related to the downregulation of circCdr1as expression [65]. In addition, circCdr1as can promote the degradation of APP and BACE1 via the proteasome and lysosome [73]. Furthermore, Dube *et al.* 2019 [52] showed that circCdr1as expression levels significantly correlate with neuropathological and clinical measures of AD severity.

It is worth noting that an age-dependent elevation of miR-138 in APP/PS1 (presenilin-1) mice. MiR-138 inhibited the expression of ADAM10 (a disintegrin and metalloproteinase domain-containing protein 10), promoted Aβ production, and induced synaptic and learning/memory deficits in APP/PS1 mice. At the same time, its suppression alleviated the AD-like phenotype in these mice. Overexpression of sirtuin 1 (Sirt1), a target of miR-138, ameliorated the miR-138-induced inhibition of ADAM10 and elevation of Aβ *in vitro*. The circRNA HDAC9 (circHDAC9) was predicted to contain a miR-138 binding site in several databases. Its expression correlated inversely with miR-138 in both Aβ-oligomer-treated N2a cells and APP/PS1 mice, and it colocalized with miR-138 in the cytoplasm of N2a cells. CircHDAC9 acted as a miR-138 sponge, decreasing miR-138 expression and reversing the Sirt1 suppression and excessive Aβ production induced by miR-138 *in vitro*. Moreover, circHDAC9 decreased in the serum of AD patients and individuals with mild cognitive impairment. It suggested that the circHDAC9/miR-138/Sirt1 pathway mediates synaptic function and APP processing in AD [85]. Recently, an alternative path of Aβ biogenesis was revealed through a circRNA harboring the Aβ-encoding region of the APP gene, termed circAβ-a, which efficiently translates into a novel Aβ175-containing Aβ polypeptide (19.2 KDa) in both cultured cells and human brain [84].

Song *et al.* 2022 [86] focused on the function of circRNA-RBP interaction in AD. CircCwc27 is a neuronal-enriched circRNA abundantly expressed in the brain and significantly upregulated in AD mice and patients. The Knockdown of circCwc27 markedly improved AD-related pathological traits and ameliorated cognitive dysfunctions. CircCwc27 directly bound to purine-rich element-binding protein A (Pur-α), increased retention of cytoplasmic Pur-α, and suppressed Pur-α recruitment to the promoters of a cluster of AD genes, including APP, dopamine receptor D1 (Drd1), protein phosphatase 1, regulatory inhibitor subunit1B (Ppp1r1b), neurotrophic tyrosine kinase, receptor, type 1 (Ntrk1), and LIM homeobox 8 (Lhx8). Downregulation of circCwc27 enhanced the affinity of Pur-α binding to these promoters, leading to altered transcription of Pur-α targets. Moreover, Pur-α overexpression largely phenocopied circCwc27 Knockdown in preventing Aβ deposition and cognitive decline [86].

The circLPAR1 was highly expressed in AD patients Wu *et al.* 2021 [87], and Li *et al.* 2020 [54] explored the underlying regulatory axis of circLPAR1, explaining how circLPAR1 can promote Aβ-induced neuronal injury. The circLPAR1 sponged on mir-212-3p led to the upregulation of its target ZNF217 and sped up apoptosis, inflammation, and oxidative stress triggered by Aβ25-35 *in vitro*. Indeed, expression levels of mir-212-3p in AD patients decreased, whereas Zinc

Finger Protein 217 (ZNF217) expression increased [87]. Moreover, the regulation of this zinc finger protein in AD was through the regulation of the lncRNA/miRNA/ZNF217 axis modulated the Aβ-induced cell injury [88] [89]. In Yang *et al.* 2019 [90] study, the circ_0000950 appeared directly involved in neuroinflammation since by sponging mir-103, it led to the expression increase of a proinflammatory gene, prostaglandin-endoperoxide synthase 2 (PTGS2), in two different *in vitro* AD models [90] [91]. The circ_0000950 enhanced neuronal apoptosis and inflammation while it reduced neurite outgrowth in AD [90].

Autophagy dysfunction represents an early neuropathological feature of AD that can affect the metabolism of Aβ and the accumulation of protein Tau [92]. In SAMP8 mice, the mmu_circRNA_017963 was highly associated with different autophagosome and vesicular transport pathways [91]. Thus, circNF1-419 increased autophagy, reducing the expression of AD markers such as Tau, p-Tau, Aβ1-42, and APOE, and ameliorated senile dementia by binding Dynamin-1 and Adaptor protein 2 B1 (AP2B1), influencing multiple signaling pathways, especially at the synapse in SAMP8 mice [93].

The brain exposed to oxidative damage affects the amyloidogenic pathway, exacerbating AD progression [94]. The involvement of circular RNA in oxidative stress AD-associated has only recently emerged [91]. mmu_circRNA_013636 and mmu_circRNA_012180 were significantly upregulated and downregulated in SAMP8 untreated mice with Panax Notogingseng Saponins (PNS). This condition was reverted under PNS treatment [91].

The circRNA, hsa_circ_0003391, which is specific and significantly downregulated in the peripheral blood of patients with AD different from other types of dementia Liu *et al.* 2020 [95], found a potential relationship between hsa_circ_0003391 and the clinical manifestation of AD. Furthermore, microRNA targeted by hsa_circ_0003391 was successfully detected, the miR-574-5p, which had an expected elevation in the AD groups, suggesting that miR-574-5p might be a potential microRNA target for hsa_circ_0003391m [95].

7. CircRNA in Autosomal Dominant Alzheimer's Disease

The expression changes in some circRNAs are a consistent phenomenon across cortical regions between AD and autosomal dominant AD (ADAD). ADAD is an early-onset AD caused by pathogenic mutations in APP, PSEN1, or PSEN237. Dube *et al.* 2019 [52] investigated whether changes in circRNA expression also occur in the context of ADAD using parietal cortex-derived, in a circular-transcriptome-wide (RNA-seq) analysis of circRNA differential expression between ADAD (n = 21) and dataset controls (n = 13), shown 236 ADAD-associated circRNAs. The authors performed a circRNA expression analysis between ADAD and AD (samples with available Braak score: nADAD = 17, nAD = 73) with a Braak score adjusted to determine if the more significant effect was related to the pathological severity in the ADAD brains. This analysis identified 77 significantly differentially expressed circRNAs, and 59 were placed in the ADAD versus control analysis. When compared to sporadic AD and controls, the gene

counts of circPSEN1 in ADAD individuals presented a significant difference [15]. Altogether, these results demonstrate that changes in circRNA expression also occur in the context of ADAD and are more severe in magnitude, even when adjusting for neuropathological severity [52].

8. Therapeutic Advantage of CircRNAs

circRNAs could be considered therapeutic agents. Covalently closed ends endow circRNAs with high stability in blood and other body fluids. Combined with controlling the expression of natural circRNAs in specific tissues and cells of the human body could reduce side effects compared to synthetic molecules, such as chemically modified drugs and RNA interference constructs, which would increase the value of circRNAs [18] [68]. Moreover, it could be a starting point for future gene therapy. To our knowledge, a general phenomenon of circRNAs, one of their primary functions is to act as a sponge for miRNAs. Thus, artificial sponges can be designed and developed by studying the endogenous structures of circRNAs to ultimately regulate the function of miRNAs in diseases. Synthetic sponges constitute a new perspective in miRNA-targeted drug development [18] [68] [96]. The advantage of circRNA therapy is its low off-target effect, unlike miRNAs and siRNAs, which exhibit more significant off-target effects at their short length. In addition to their high stability, specificity, structure, and mechanisms of action, circRNAs are suitable biomarkers for diagnosis and disease progression.

9. Conclusions

Given the global increase in neurodegenerative diseases, sustained efforts are being made to search for diagnostic and prognostic RNA markers. circRNAs could represent reliable and affordable candidates. First, they show advantages over linear RNAs; circRNAs are more resistant to exonuclease than the linear transcript and are, therefore, more stable in cells. Their peculiar structure distinguishes them from linear RNAs. They accumulate, especially in the brain, in an age-dependent manner, making them even more attractive for neurodegenerative biomarker research.

Furthermore, their ability to cross the BBB and their highly tissue-specific expression is unrelated to their cognate linear RNAs. In addition, high blood and other body fluids stability make them even more interesting for neurodegenerative disease biomarker research and as targets for molecular therapies. Although the search for circRNA-specific biomarkers in neurodegenerative diseases is still in its early stages, the observation that circRNAs differentially expressed in the brain overlap with circRNAs in the plasma of patients affected by neurodegenerative diseases suggests an encouraging use as peripheral biomarkers. Notwithstanding growing evidence highlighting the increased potency and potential of circRNAs, a deeper understanding of their molecular mechanisms under both physiological and pathological conditions is required. The fast advance in

next-generation RNA sequencing and bioinformatics allowed the discovery of thousands of circRNAs, challenging our understanding of gene expression regulation.

Conflicts 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.

Author Contributions

CREA, JAMA, PCML, and MRMA: collected, analyzed, and summarized the current literature. CREA and MRMA wrote the article.

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