We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Chapter

The circRNA and Role in Alzheimer's Disease: From Regulation to Therapeutic and Diagnostic Targets

Wen Li and Guohua Jin

Abstract

Alzheimer's disease (AD) is a devastating neurodegenerative disorder and the most common form of dementia worldwide. Although the great progress on the prevention and treatment of AD, no effective therapies are available as yet. With the increasing incidence of AD, it has brought a growing burden to the family and society. Histopathologically, AD is characterized by the presence of myloid β (Aβ) plaques composed of Aβ and neurofibrillary tangles (NFTs) composed of hyper-phosphorylated tau proteins, which lead to neuronal loss. However, the full spectrum of precise molecular mechanism that contribute to AD pathogenesis remains largely unknown. circular RNAs (circRNAs) are a novel class of endogenous non-coding RNAs that play a vital role in post-transcriptional regulation. Recent reports showed circRNAs to be an important player in the development of neurodegenerative diseases like AD. In this chapter, we review recent progress on understanding the role of circRNAs in AD, and many studies implicating specific circRNAs in the development of the disease. Moreover, we explore the potential promise of these findings for future diagnosis and treatment.

Keywords: Alzheimer's disease, circular RNA, molecular mechanism, therapy

1. Introduction

Non-coding RNAs (ncRNAs) are a broad spectrum of functional RNA molecules that are transcribed from DNA but not translated into proteins [1]. The discovery of microRNAs (miRNAs) in 1993 followed by developments and discoveries in small RNA biology have hinted the importance of RNA in the post-transcriptional regulation of genes, especially in eukaryotes [2, 3]. With the development of high-throughput RNA sequencing technologies and bioinformatics methods, thousands of new ncRNAs have been discovered. Circular RNAs (circular RNAs, circRNAs) are a novel class of highly conservative endogenous ncRNA generated by pre-mRNA back splicing, which is characterized by a covalently closed-loop structure (**Figure 1**) [4]. It was originally discovered that circRNAs are universally present in human and mouse, but then they were found to be common across essentially all eukaryotes [5]. Although most circRNAs are generally expressed at low levels, some of them are more abundant than their linear counterparts and often exhibit
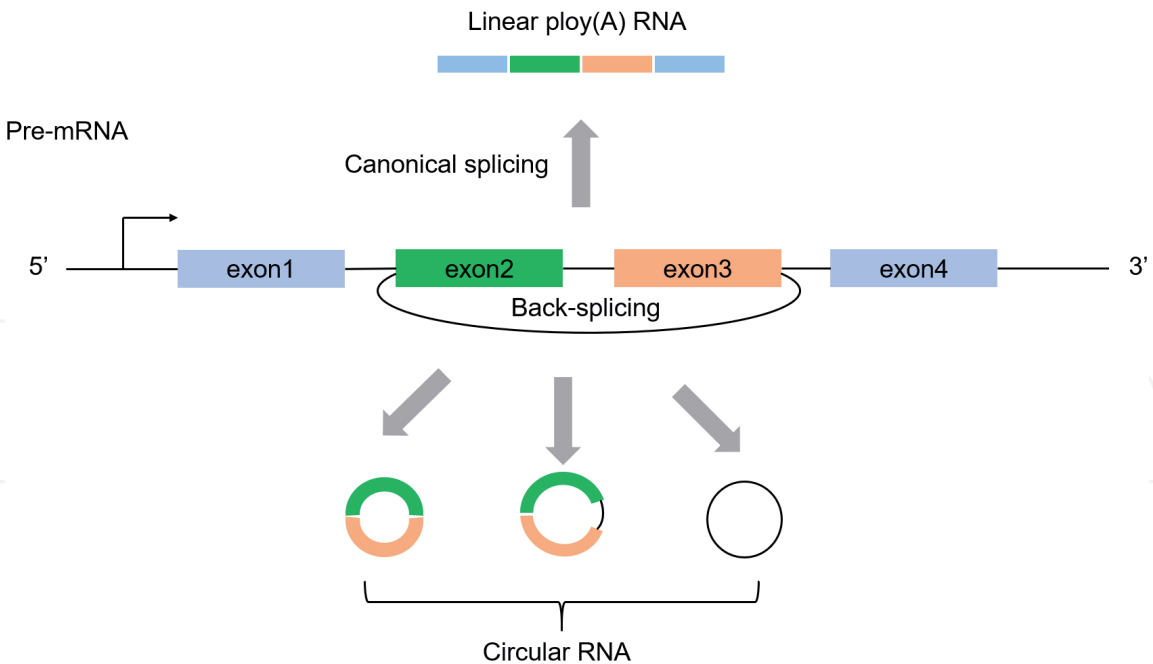
Figure 1.
Back-splicing and canonical splicing of a single pre-mRNA.

cell-type-specific and tissue-specific patterns [6, 7]. CircRNA levels are highly enriched in the brain, both embryonic and adult stage, and many of them play important roles in synaptic plasticity and neuronal function [8, 9]. Accumulating data suggest key roles for circRNAs in Alzheimer's disease (AD) by affecting mechanisms such as neuronal plasticity, autophagy, apoptosis, and inflammation [10]. This review covers the expression and function of circRNAs in the brain, as well as their role involvement in initiation and progression of AD.

2. Characteristics of circRNAs

2.1 Abundance of circRNAs

In the 1970s, circRNAs were first discovered in eukaryotic cytoplasm, but due to their low abundance and circular isoforms, these RNAs were perceived as mis-splicing occurrences [11]. With the advancement of high-throughput sequencing technology, circRNAs have been found to be abundant and widespread not only in metazoans including mice, Drosophila, and zebrafish but also in protists, fungi, and plants [7]. Although most of these covalently linked transcripts generally are expressed at low levels, in some cases, their abundance can exceed that of related linear mRNAs due to higher expression accumulation [12, 13]. For example, the expression of CDR1as within the brain is highly and independent of the expression of its linear isoform [14]. You et al. [15] discovered that the expression of some circRNAs exhibited strong up-regulation in brain during development, and their expression independent of their host linear transcripts. Jeck et al. [16] found that the abundance of some circRNAs exceeded associated linear mRNA by >10-fold in human fibroblasts.

2.2 Stability of circRNAs

CircRNAs are found mostly in the cytoplasm, and most undesired splicing products accumulate at the transcription site [17]. Because they do not have 5′-3′ polarities and polyadenylated tails, which make them much more stable than

linear RNA and resistant to RNase R, an exonuclease that efficiently degrades linear RNAs [13]. The average half-life of circRNAs in cells exceeds 48 hours, while mRNAs only maintaine for the average of 10 hours [14]. Besides, circRNAs may also be sensitive to many other RNases, such as RNase A, RNase T1, and RNase T2 [18], which suggests that circRNA may serve as an ideal biomarker for a variety of disease. Recent studies have shown that circRNAs are enriched and stable in exosomes, which can be transported to distant tissues and organs via exosomes [19]. Moreover, circRNAs can be detected in blood cells like red blood cells, white blood cells, and platelets [20]. Besides blood, circRNAs can also be detected in other bodily fluids, such as saliva and seminal plasma [14, 21].

2.3 Profile and localization of circRNA

The expression of circRNA has tissue specificity, subcellular location specificity and developmental stage specificity. It is reported that circRNAs in *Drosophila*, mice, and humans are highly enriched in the nervous system [22]. RNA sequencing of human adult and fetal tissues showed that up to 50% of circRNAs were tissue-specific and development-specific fashion, and the number and expression levels of circRNAs were higher in fetal tissue than adult tissue [23]. Notably, the expression of circRNAs within the brain is highly specific and increases during neuronal differentiation and development, which may be involved in brain diseases [24]. CircRNAs are mostly found in the cytoplasm, and many of them in neurons localized to axons, dendrites, and synaptosomes, which is modulated by neuronal activity [15]. Reports show that compared with total brain RNA, circRNAs in murine synaptoneurosome fractions and micro-dissected neuropil from hippocampal slices were more enriched in cytoplasmic RNA [25]. This is supported by the detection of circRNAs in cultured hippocampal neurons and hippocampal slices [15]. Moreover, some circRNAs show a regulated switch in their nuclear and cytoplasmic positioning during development [24].

2.4 Classification of circRNAs

According to different combinations of sequences and domains, circRNAs can be divided into three categories: exonic circRNAs (EciRNAs), intronic circRNAs (CiRNAs) and exon-intron circRNAs (EIciRNA) (**Figure 2**) [26]. There are three hypothetical models explaining the formation of exonic circRNAs. Most circRNAs are formed by exon skipping during pre-mRNA transcription to produce specific regions, called lariat structures. Lariat structures contain exons, in which the intron sequence is then removed by splicing [27]. Other than exon skipping, due to the presence of reverse complement sequences in introns of pre-mRNA, circular structures can be formed by base-pairing between two introns, and some introns are then removed [28].

During the biogenesis of circRNAs, some RNA binding proteins (RBPs) are considered to participate in the circularization of circRNA, such as Quaking, Muscleblind and Fused-in sarcoma [29]. In some cases, during the formation of EciRNAs, introns that surround the exons are not removed, and EIciRNAs are generated [30]. The formation of CiRNAs depends on a consensus motif containing a conserved 7-nucleotide GU-rich motif at the 5′ splicing site and the 11-nucleotide C-rich motif at the 3′-branch site. it bypasses the action of the debranching enzyme, then generates a linear intron and form a circularized RNA lariat, leading to the production of ciRNA [9, 31]. EciRNAs mainly locate in the cytoplasm, which is the focus of current research, accounting for almost 80% of the total circRNAs [6]. CiRNAs and EIciRNAs locate in the nucleus, and regulate the expression of their parental genes [32].
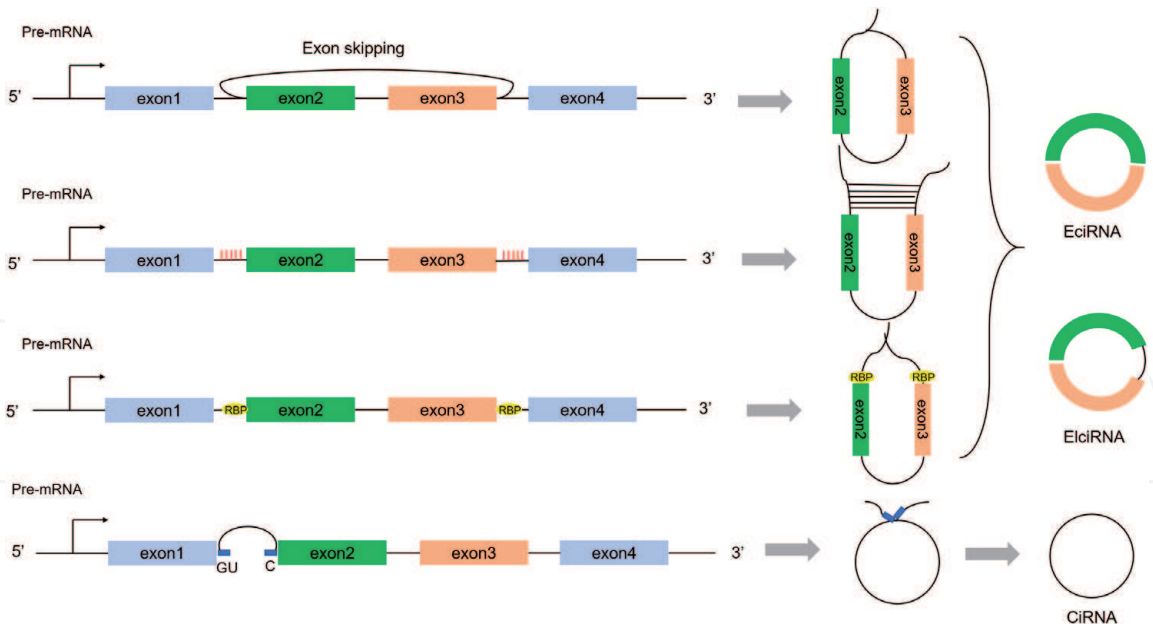
Figure 2.
Formation and classification of circRNAs.

3. Biological functions of circRNAs

circRNAs play key role in gene regulation at the post-transcriptional or transcription level, thereby affecting the level of gene expression. Here, we will introduce how circRNAs work at the molecular level and the underlying mechanisms involved in the interaction with other molecules (**Figure 3**).

3.1 circRNAs can act as microRNA (miRNA) sponges

Some long non-coding RNAs were described as a sponge for miRNAs, which can regulate the level or activity of miRNAs by selective sponging [33]. It was
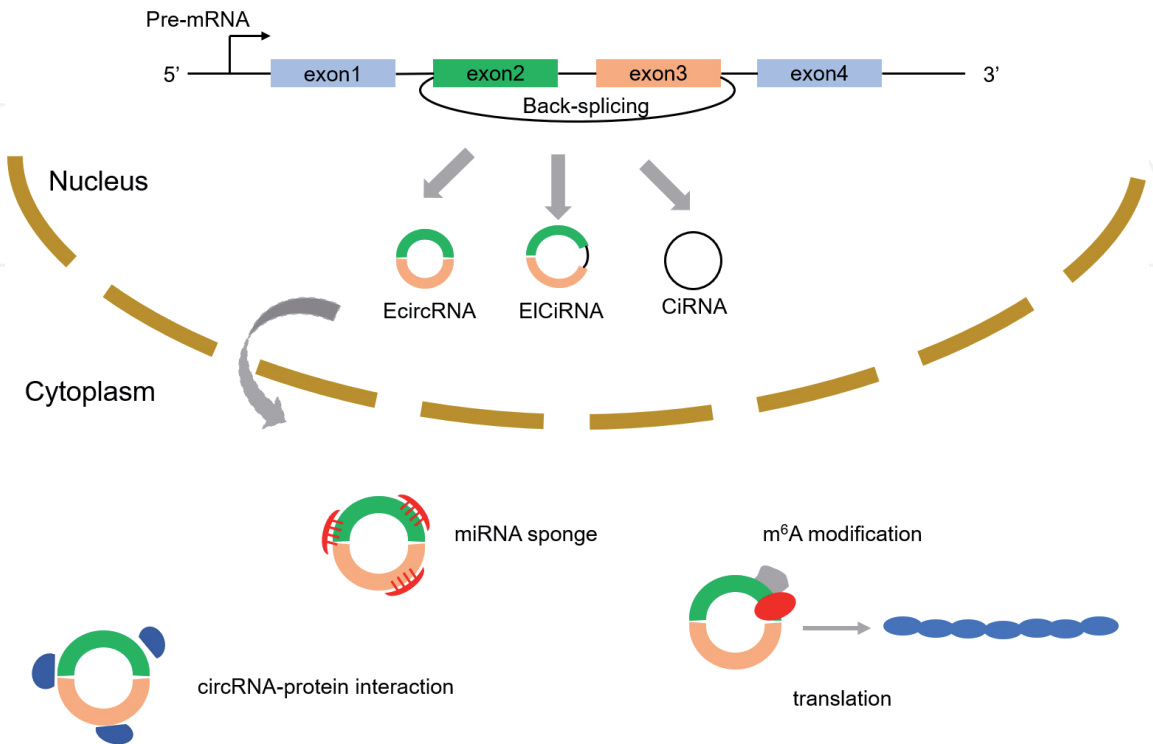

Figure 3.
Functions of circRNAs.

initially observed that some circRNAs have many miRNA-binding sites, leading to speculation that these molecules could act as miRNA sponges. Some circRNAs possess multiple binding sites for specific miRNAs, and some circRNAs harbor many different types of miRNA binding sites. For example, circRNA Cdr1as (ciRS-7) is extensively expressed in the mammalian brain and upregulated during neuronal development, which harbors 74 seed binding sites for miR-7 [34]. Intriguingly, miR-7 has been implicated, as a key regulator to modulate the expression of several oncogenes [35] and hold potential for slowing Parkinson's disease (PD) progression [36]. Similarly, circ-SRY (sex-determining region Y), is a master regulator of mammalian sex determination and specifically expressed in testis, which has 16 binding sites for miR-138 [37, 38]. Additionally, circHIPK3 is observed to sponge to 9 miRNAs with 18 potential binding sites [39]. cir-ITCH may act as a sponge of miR-7, miR-17, and miR-214 [40]. circHIPK3 was reported to bind to miR-124, miR-30a, and miR-558 [39, 41, 42]. So far, circRNA-miRNA axis in diseases have been expanded [43], and can be used as an advanced molecular technology to simulate or manufacture therapeutic agents, which indicates that this regulatory function of circRNAs should be a hotspot in the field of RNA. For instance, circHomer1 is upregulated in Hepatocellular carcinoma and regulates cell proliferation, migration, and invasion by inhibition of miR-1322 [44]. circTLK1 is upregulated during the acute period after focal ischemia, which can be functioned as an endogenous miR-335-3p sponge, leading to neuronal injury and neurological deficits [45]. Through deep RNA sequencing, novel_circ_0003012 and mmu-miR-298-3p were identified dysregulated in the hippocampus of APP/PS1 mice. Besides, novel_circ_0003012/mmu-miR-298-3p axis may regulate the pathological mechanism of AD by the cGPM-PKG signaling pathway [46].

3.2 circRNAs can interact with proteins

The most well-known proteins interacting with RNA molecules are the RBPs. RBPs are a large class of over 2000 proteins, that interact with transcripts to participate in forming ribonucleoprotein (RNP) complexes to influence the RNA fate [47]. Many circRNAs are predicted to interact with RBPs, although bioinformatic analyses of circRNA sequences revealed very little enrichment in binding sites of RBPs [48]. Human antigen R (HuR), an extensively studied RBP, regulates protein expression patterns by associating with a wide range of noncoding RNAs (ncRNAs), including miRNAs, long ncRNAs (lncRNAs), and circRNAs [49]. Li et al. [50] found that circPABPN1 blocked HuR binding to Atg16l1 mRNA, and represses HuR-induced ATG16L1 translation, thereby modulating Autophagy in the Intestinal Epithelium. Chen et al. [51] showed that oncogenic circAGO2 physically interacts with HuR, resulting in repression of AGO2/miRNA-mediated gene silencing during cancer progression. Quaking (QKI) is a member of the STAR family of KH domain-containing RNA-binding proteins, which is involved in pre-mRNA splicing, microRNA regulation, and formation of circRNA [52]. Gupta et al. [53] found that overexpression of Quaking 5 (Qki5) strongly attenuates doxorubicin-induced apoptosis and atrophy in cardiomyocytes via regulating a set of cardiac circRNAs. Zhu et al. [54] discovered that Qki5 is significantly downregulated in Hepatocellular carcinoma tissues, leading to the reduction of circZKSCAN1. Furthermore, circ-Foxo3 was observed to function as a scaffold to regulate the expression of its binding proteins by modulating protein–protein interaction. For example, circ-Foxo3 interacts with p21 and CDK2, promoting the inhibition of CDK2 by p21, and regulating cell cycle progression [17]. circ-Foxo3 can bind to p53 and Mdm2, to promote Mdm2-induced p53 ubiquitination and subsequent degradation, resulting in increased levels of Foxo3 protein [48]. circ-Foxo3 can interact with

ID-1, E2F1, FAK, and HIF1α, leading to these proteins retaining in the cytoplasm and no longer exerting their anti-senescent and anti-stress roles [55].

3.3 m⁶A modification regulates circRNA translation

N6-methyladenosine (m^{6}A), the most prevalent internal RNA modification in mammalian cells, regulates RNA transcription, processing, splicing, degradation, and translation [56–58]. m^{6}A modification occurs by RNA methylation on the sixth N atom of adenylate (A) in RNAs [59]. m^{6}A modification sites tend to be found in the stop codon and 3′ untranslated region with a consensus sequence RRACH (in which R represents A or G and H represents A, C or U) [60]. The regulation function of m^{6}A is consisted of three factors referred to as "writers", "erasers" and "readers" [61]. m^{6}A "writers" are proteins involved in the formation of the methyltransferase complex, including methyltransferase-like 3/14/16 proteins (METTL3/14/16), Wilms tumor 1-associated protein (WTAP), RNA-binding motif protein 15/15B (RBM15/15B), and Vir-like m^{6}A methyltransferase associated (VIRMA, also known as KIAA1429) [62, 63].

m^{6}A methylation is dynamic and, and can be reversed by some demethylases (erasers). Erasers include FTO and AlkB homolog 3/5 (ALKBH3/5) [63, 64]. m^{6}A regulates gene expression through m^{6}A recognition factors, known as "readers," including YT521-B homology YTH domain family (YTHDF1/2/3), YTH domain containing 1 (YTHDC1/2), heterogeneous nuclear ribonucleoproteins (HNRNPs), eukaryotic translation initiation factor 3 (eIF3), and insulin-like growth factor-2 mRNA-binding proteins 1/2/3 (IGF2BP1/2/3) [61, 65].Recent studies have identified that m6A-modified circRNAs are related with pathophysiological processes. For example, m6A-modified RNA immunoprecipitation sequencing (m6A-RIP-seq) and RNA sequencing (RNA-seq) revealed the level of m6A abundance in total circRNAs was decreased in the lens epithelium cells (LECs) from cortical type of ARCs (ARCCs), and ALKBH5 was significantly upregulated [66]. Sun et al. [67] found that.

m6A modification are present on circPVRL3, which promoted gastric cancer cell proliferation. Huang et al. [68] found that circSTAG1 can bind ALKBH5 to inhibit its nuclear entry and increase the level of m6A modification of RNA, which attenuated depressive-like behaviors.

4. Role of circRNAs in AD

There is rising recognition that ncRNAs differences in the context of AD have yielded insight into the pathogenic mechanisms underlying this disease as well as biomarkers and potential therapeutic targets. Here, we provide the latest information on potential circRNAs involved in AD pathology.

4.1 AD pathogenesis

Reported histopathological characteristics of AD are Aβ plaques and NFTs, composed of Aβ protein accumulation and phosphorylated tau protein (p-tau) [69].

Amyloid pathogenesis starts with altered cleavage of amyloid precursor protein (APP) by β-secretases (BACE1) and γ-secretases, leading to the production of Aβ, which is then dumped into the extracellular space [70]. Consequently, accumulating Aβ forms Aβ oligomers and gradually polymerizes into amyloid fibrils that aggregate into plaques [71]. Tau is a microtubule-associated protein in neurons and

plays an important role in maintaining the stability of microtubules [72]. Abnormal phosphorylation of tau makes it insoluble, reduces its ability to bind tubulin and promote microtubule assembly, and makes it self-associate into paired helical filament [73]. Additionally, microgliosis is consistently found around plaques in the brain [74]. This facilitates microglial activation and inflammatory response, and contributes to neuritic damage.

4.2 Aβ production and clearance in AD

Except for some antisense transcripts and microRNAs involved in accumulation, oligomerization, aggregation and formation of Aβ plaques, recent studies have shown that circRNAs may play a role in the of production and clearance Aβ [75, 76]. For example, circHDAC9 acted as a miR-138 sponge, decreasing miR-138 expression, Inhibiting the production of Aβ, and alleviating synaptic and learning/memory deficits in APP/PS1 mice. Moreover, circHDAC9 was remarkably decreased in the serum of both mild cognitive impairment and AD patients [77]. Shi et al. [78] found that ciRS-7 promotes the expression of UCHL1, reduces the protein levels of APP and BACE1 by promoting their degradation, and inhibits translation of NF-κB, thereby reducing the generation of Aβ. Shi et al. [79] demonstrated that circAβ-a, containing the corresponding Aβ coding sequence, served as a template for the synthesis of a novel Aβ-containing Aβ175 polypeptide in both cultured cells and human brain. Utilizing deep RNA sequencing, Zhang et al. [80] observed that there are 235 significantly dysregulated circRNA transcripts in a 7-month-old senescence-accelerated mouse prone 8. Additionally, circRNA-related ceRNA networks in this AD mouse model were mainly involved in the regulation of Aβ clearance.

4.3 Neuroinflammation in AD

A number of studies have proven that in addition to Aβ and NFTs, neuroinflammation is exhibited in the brains of AD patients and contributes to the pathogenesis of this disease [81, 82]. Not only Aβ can activate the microglia, but also Tau protein can trigger inflammation through interaction with microglia. Due to the accumulation of Aβ and hyperphosphorylation of Tau, microglia are persistently activated, which produce inflammatory cytokines and chemokines, contributing to the neuroinflammation process [81, 83]. For instance, TNF-α can stimulate γ-secretase activity, which results in increased levels of Aβ and the following cognitive decline in AD [84]. IL-1 increases generation of Aβ and phosphorylation of tau protein, leading to dysfunction of the cholinergic system [85]. Studies have shown that CCL2 and CCL5 expression are increased in the AD brain. Up to now, there are few reports in this field. Wang et al. [86] found that in OGD-activated microglia, circPTK2 regulates neuronal apoptosis via sponging miR-29b. it can be inferred that circRNAs may be involved in the activation of AD microglia. One study on circRNAs involved in neuroinflammation indicates that circ_0000950 inhibits miR-103 expression and increases prostaglandin-endoperoxide synthase 2 (PTGS2) expression in AD models. Moreover, circ_0000950 promotes neuron apoptosis, neurite outgrowth, and affects the level of IL-1β, IL-6 and TNF-α via directly sponging miR-103 in AD [87].

4.4 Oxidative stress in AD

Emerging evidences demonstrate that oxidative stress has been recognized as a contributing factor in the progression of AD. It has been confirmed that elevated levels of Aβ are associated with increased levels of oxidation products, and protein and lipid oxidation was observed in brain regions rich in Aβ [88, 89]. Moreover,

due to the role of protein Tau both in the modulation microtubule dynamics and morphology and physiology of neurons, Tau alteration would constitute to a target for oxidative stress in AD [90, 91]. Recently, important regulatory roles of some circRNAs in the oxidative stress have been identified. Previous studies have shown that panax notoginseng saponins (PNS) could protect neurons in AD brain from oxidative stress damage injury via attenuating the production of 8-hydroxydeoxy-guanosine (8-OHdG), enhancing the expressions and activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-PX) [92]. Through circRNA Microarray, it was found that PNS treatment leads to five circRNAs upregulation and two circRNAs downregulation. Next, mmu_circRNA_013636 and mmu_circRNA_012180 were selected, and GO and KEGG analyses were showed that mmu_circRNA_013636 and mmu_circRNA_012180 were involved in AD-associated biological process [93]. Based on these results, the mmu_circRNA_013636 and mmu_circRNA_012180 may be associated with the mechanisms by which PNS attenuates AD progression, and may be highly related to the regulation of oxidative stress. Zhu et al. [94] found that the expression level of circular ribonucleic acid 0001588 was suppressed in model of AD, which promoted cell growth, reduced levels of lactate dehydrogenase, caspase-3, and caspase-9. Besides, circular ribonucleic acid 0001588 reduced reactive oxygen species production via activation of the silent information regulator 1 pathway.

4.5 Autophagy in AD

Substantial studies reveal that deficits in autophagy are involved in AD pathogenesis. Defective autophagy and mitophagy, which is responsible for synaptic dysfunction and cognitive deficits, are triggered by Aβ and Tau accumulation [95]. Recently, several reports have described potential roles for circRNAs in autophagosome assembly or vesicular transport-mediated pathways [96]. For example, Chen et al. [97] found that circNF1–419 regulates autophagy through PI3K-I/Akt-AMPK-mTOR and PI3K-I/Akt–mTOR signaling pathways, and reduces the expression of AD marker proteins Tau, p-Tau, Aβ1–42, and APOE in AD-like mice. Using circRNA microarray, GO analysis revealed that mmu_circRNA_017963 is highly associated with autophagosome assembly, exocytosis, apoptotic process, transport and RNA splicing in an AD mouse model. Moreover, KEGG pathway analysis indicated that mmu_circRNA_017963 was strongly related with synaptic vesicle cycle, spliceosome, glycosaminoglycan, and SNARE interactions in vesicular transport [98]. All of these biological processes are reported to play an important role in the development of AD [98, 99].

4.6 Therapeutic targets and diagnostic biomarkers in AD

Due to the high stability with covalently closed continuous loop, circRNAs are not sensitive to ribonucleases, such as RNase R, and have a longer half-life compared to linear RNAs [100]. An accumulating number of studies have shown that dysregulated circRNAs are significantly related to AD, which are considered to be potential biomarkers. For instance, Dube et al. [101] found that circRNA expression significantly associated with the diagnosis of AD, the severity of clinical dementia, and the severity of neuropathology. Lo et al. [102] profiled circRNA expression at different AD stages in brain samples from four brain regions: anterior prefrontal cortex, superior temporal lobe, parahippocampal gyrus and inferior frontal gyrus using a public RNA-sequencing dataset. There are 147 differentially expressed circRNAs to be found in the four regions, and most circRNAs in AD patients with severe symptoms are enriched in the parahippocampal gyrus. This

finding could help to distinguish the disease severity of patients, and further implying that circRNAs may serve as biomarkers of AD. In addition, circRNAs can stably exist in blood plasma and cerebrospinal fluid. Liu et al. [103] discovered that hsa_circ_0003391 is significantly downregulated in the peripheral blood, and closely related to clinical features of patients with AD. By microarray, Li et al. [104] found 112 circRNAs were upregulated and 51 circRNAs were downregulated in cerebrospinal fluid of AD patients. Among the up-regulated circRNAs, circ-AXL was negatively correlated with Aβ42 and positively correlated with t-Tau and p-tau, suggesting it hold the clinical value for predicting disease risk and disease severity of AD. Moreover, research on circRNAs sponges may help to design and develop effective artificial sponges to regulate disease progression. As a stable and effective miRNA inhibitor, artificial miRNA sponge technology may be a new strategy for RNA gene therapy in the future.

5. Conclusions and future perspectives

circRNAs have gained increased attention because of their involvement in different biological processes. With the rapid progress of high throughput sequencing and bioinformatics technology, multiple circRNAs have demonstrated to be closely associated with various diseases. Although the function and modulation of circRNA has not been clearly understood, studies have started to excavate effect of AD-related circRNAs, which brought us many surprising findings. As a class of stable RNA, circRNAs have natural advantages and may play vital roles as therapeutic targets and prognostic factors for AD. Recently, with the emergence of CRISPR-Cas13d screening tools [105], lipid nanoparticle (LNP) delivery system [106], the in vitro engineered preparation of circRNA can be realized, and make the application of circRNA in clinical therapy possible. In addition, Lavenniah et al. [107] constructed a circmiR sponge targeting the known cardiac pro-hypertrophic miRs-132 and miRs-212, and delivered it to cardiomyocytes *in vivo by* Adeno-associated viruses (AAVs). Subsequently, the hypertrophic characteristics of the disease were attenuated, thus supporting the therapeutic potential of Engineered circRNAs. However, there are some some questions that deserve attention. Firstly, most of the current studies on circRNAs rely on the results of RNA-sequencing and microarray. There are significant differences between the output of different algorithms, emphasizing that these circRNAs need urther validation. Secondly, many circRNAs have been identified to be differentially expressed at different developmental stages, but the precise mechanisms are still not clear. Thirdly, at present, most studies on circRNAs mainly focus on miRNA sponge, and there are few studies on other mechanisms. In conclusion, circRNA research is still in its infancy and their molecular mechanism and functional role need to be further elucidated. circRNAs are widely involved in the regulation of physiological and pathophysiological processes, and may have the potential to be new biomarkers and novel therapeutic targets.

Author details

Wen Li[1,2,3]* and Guohua Jin[1,2,3]

1 Department of Human Anatomy, Institute of Neurobiology, Medical School of Nantong University, Nantong, Jiangsu, P.R. China

2 Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Nantong, Jiangsu, P.R. China

3 Co-Innovation Center of Neuroregeneration, Medical School of Nantong University, Nantong, Jiangsu, P.R. China

*Address all correspondence to: 1554371938@qq.com

IntechOpen

References

[1] Poller W, et al. Non-coding RNAs in cardiovascular diseases: diagnostic and therapeutic perspectives. Eur Heart J, 2018, 39(29): 2704-2716.

[2] Lee RC, Feinbaum RL, and Ambros V. The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell, 1993, 75(5): 843-854.

[3] Yang JD, Liu MC, and Kisiel JB. Circulating Tumor DNA and Hepatocellular Carcinoma. Semin Liver Dis, 2019, 39(4): 452-462.

[4] Wu X, et al. Circular RNA: A novel potential biomarker for skin diseases. Pharmacol Res, 2020, 158(104841.

[5] Salzman J. Circular RNA Expression: Its Potential Regulation and Function. Trends Genet, 2016, 32(5): 309-316.

[6] Zhang P, et al. Circular RNA Regulation of Myogenesis. Cells, 2019, 8(8):

[7] Li X, Yang L, and Chen LL. The Biogenesis, Functions, and Challenges of Circular RNAs. Mol Cell, 2018, 71(3): 428-442.

[8] Hanan M, Soreq H, and Kadener S. CircRNAs in the brain. RNA Biol, 2017, 14(8): 1028-1034.

[9] Mehta SL, Dempsey RJ, and Vemuganti R. Role of circular RNAs in brain development and CNS diseases. Prog Neurobiol, 2020, 186(101746.

[10] Zhang Y, et al. Exploring the regulatory roles of circular RNAs in Alzheimer's disease. Transl Neurodegener, 2020, 9(1): 35.

[11] Sanger HL, et al. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc Natl Acad Sci U S A, 1976, 73(11): 3852-3856.

[12] Greene J, et al. Circular RNAs: Biogenesis, Function and Role in Human Diseases. Front Mol Biosci, 2017, 4(38.

[13] Xiao MS, Ai Y, and Wilusz JE. Biogenesis and Functions of Circular RNAs Come into Focus. Trends Cell Biol, 2020, 30(3): 226-240.

[14] Li HM, Ma XL, and Li HG. Intriguing circles: Conflicts and controversies in circular RNA research. Wiley Interdiscip Rev RNA, 2019, 10(5): e1538.

[15] You X, et al. Neural circular RNAs are derived from synaptic genes and regulated by development and plasticity. Nat Neurosci, 2015, 18(4): 603-610.

[16] Jeck WR, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA, 2013, 19(2): 141-157.

[17] Du WW, et al. Identifying and Characterizing circRNA-Protein Interaction. Theranostics, 2017, 7(17): 4183-4191.

[18] Vincent HA and Deutscher MP. Substrate recognition and catalysis by the exoribonuclease RNase R. J Biol Chem, 2006, 281(40): 29769-29775.

[19] Kim KM, et al. RNA in extracellular vesicles. Wiley Interdiscip Rev RNA, 2017, 8(4):

[20] Ouyang Q, et al. Microarray Expression Profile of Circular RNAs in Peripheral Blood Mononuclear Cells from Rheumatoid Arthritis Patients. Cell Physiol Biochem, 2017, 42(2): 651-659.

[21] Jafari Ghods F. Circular RNA in Saliva. Adv Exp Med Biol, 2018, 1087(131-139.

[22] Zheng S, et al. CircRNA-Protein Interactions in Muscle Development and Diseases. Int J Mol Sci, 2021, 22(6):

[23] Xu T, et al. Circular RNA expression profiles and features in human tissues: a study using RNA-seq data. BMC Genomics, 2017, 18(Suppl 6): 680.

[24] Patop IL, Wust S, and Kadener S. Past, present, and future of circRNAs. EMBO J, 2019, 38(16): e100836.

[25] Rybak-Wolf A, et al. Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. Mol Cell, 2015, 58(5): 870-885.

[26] Ma S, et al. CircRNAs: biogenesis, functions, and role in drug-resistant Tumours. Mol Cancer, 2020, 19(1): 119.

[27] Ma Y, Liu Y, and Jiang Z. CircRNAs: A new perspective of biomarkers in the nervous system. Biomed Pharmacother, 2020, 128(110251.

[28] Fang Z, Jiang C, and Li S. The Potential Regulatory Roles of Circular RNAs in Tumor Immunology and Immunotherapy. Front Immunol, 2020, 11(617583.

[29] Tang X, et al. Review on circular RNAs and new insights into their roles in cancer. Comput Struct Biotechnol J, 2021, 19(910-928.

[30] Shang Q, et al. The novel roles of circRNAs in human cancer. Mol Cancer, 2019, 18(1): 6.

[31] Li J, et al. CircRNAs: a new target for the diagnosis and treatment of digestive system neoplasms. Cell Death Dis, 2021, 12(2): 205.

[32] Floris G, et al. Regulatory Role of Circular RNAs and Neurological Disorders. Mol Neurobiol, 2017, 54(7): 5156-5165.

[33] Han TS, et al. Epigenetic Associations between lncRNA/circRNA and miRNA in Hepatocellular Carcinoma. Cancers (Basel), 2020, 12(9):

[34] Guo Z, et al. Biogenesis, Features, Functions, and Disease Relationships of a Specific Circular RNA: CDR1as. Aging Dis, 2020, 11(4): 1009-1020.

[35] Hansen TB, Kjems J, and Damgaard CK. Circular RNA and miR-7 in cancer. Cancer Res, 2013, 73(18): 5609-5612.

[36] D'ambra E, Capauto D, and Morlando M. Exploring the Regulatory Role of Circular RNAs in Neurodegenerative Disorders. Int J Mol Sci, 2019, 20(21):

[37] Hansen TB, et al. Natural RNA circles function as efficient microRNA sponges. Nature, 2013, 495(7441): 384-388.

[38] Zhao ZJ and Shen J. Circular RNA participates in the carcinogenesis and the malignant behavior of cancer. RNA Biol, 2017, 14(5): 514-521.

[39] Zheng Q, et al. Circular RNA profiling reveals an abundant circHIPK3 that regulates cell growth by sponging multiple miRNAs. Nat Commun, 2016, 7(11215.

[40] Li F, et al. Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/beta-catenin pathway. Oncotarget, 2015, 6(8): 6001-6013.

[41] Chen B, et al. Circular RNA circHIPK3 Promotes the Proliferation and Differentiation of Chicken Myoblast Cells by Sponging miR-30a-3p. Cells, 2019, 8(2):

[42] Li Y, et al. CircHIPK3 sponges miR-558 to suppress heparanase expression in bladder cancer cells. EMBO Rep, 2017, 18(9): 1646-1659.

[43] Su Q and Lv X. Revealing new landscape of cardiovascular disease through circular RNA-miRNA-mRNA axis. Genomics, 2020, 112(2): 1680-1685.

[44] Zhao M, et al. Circ-HOMER1 enhances the inhibition of miR-1322 on CXCL6 to regulate the growth and aggressiveness of hepatocellular carcinoma cells. J Cell Biochem, 2020, 121(11): 4440-4449.

[45] Wu F, et al. Circular RNA TLK1 Aggravates Neuronal Injury and Neurological Deficits after Ischemic Stroke via miR-335-3p/TIPARP. J Neurosci, 2019, 39(37): 7369-7393.

[46] Zhang Y, et al. CircRNA-ceRNA Network Revealing the Potential Regulatory Roles of CircRNA in Alzheimer's Disease Involved the cGMP-PKG Signal Pathway. Front Mol Neurosci, 2021, 14(665788.

[47] Schuschel K, et al. RNA-Binding Proteins in Acute Leukemias. Int J Mol Sci, 2020, 21(10):

[48] Huang A, et al. Circular RNA-protein interactions: functions, mechanisms, and identification. Theranostics, 2020, 10(8): 3503-3517.

[49] Abdelmohsen K, et al. Identification of HuR target circular RNAs uncovers suppression of PABPN1 translation by CircPABPN1. RNA Biol, 2017, 14(3): 361-369.

[50] Li XX, et al. Interaction between HuR and circPABPN1 Modulates Autophagy in the Intestinal Epithelium by Altering ATG16L1 Translation. Mol Cell Biol, 2020, 40(6):

[51] Chen Y, et al. Circular RNA circAGO2 drives cancer progression through facilitating HuR-repressed functions of AGO2-miRNA complexes. Cell Death Differ, 2019, 26(7): 1346-1364.

[52] Chen X, et al. The Emerging Roles of the RNA Binding Protein QKI in Cardiovascular Development and Function. Front Cell Dev Biol, 2021, 9(668659.

[53] Gupta SK, et al. Quaking Inhibits Doxorubicin-Mediated Cardiotoxicity Through Regulation of Cardiac Circular RNA Expression. Circ Res, 2018, 122(2): 246-254.

[54] Zhu YJ, et al. Circular RNAs negatively regulate cancer stem cells by physically binding FMRP against CCAR1 complex in hepatocellular carcinoma. Theranostics, 2019, 9(12): 3526-3540.

[55] Du WW, et al. Foxo3 circular RNA promotes cardiac senescence by modulating multiple factors associated with stress and senescence responses. Eur Heart J, 2017, 38(18): 1402-1412.

[56] Chen M and Wong CM. The emerging roles of N6-methyladenosine (m6A) deregulation in liver carcinogenesis. Mol Cancer, 2020, 19(1): 44.

[57] Cheng M, et al. The m(6)A methyltransferase METTL3 promotes bladder cancer progression via AFF4/NF-kappaB/MYC signaling network. Oncogene, 2019, 38(19): 3667-3680.

[58] Barbieri I, et al. Promoter-bound METTL3 maintains myeloid leukaemia by m(6)A-dependent translation control. Nature, 2017, 552(7683): 126-131.

[59] Zhou P, et al. Meclofenamic acid promotes cisplatin-induced acute kidney injury by inhibiting fat mass and obesity-associated protein-mediated m(6)A abrogation in RNA. J Biol Chem, 2019, 294(45): 16908-16917.

[60] Li Y, et al. The dynamics of FTO binding and demethylation from the m(6)A motifs. RNA Biol, 2019, 16(9): 1179-1189.

[61] Liu ZX, et al. Link Between m6A Modification and Cancers. Front Bioeng Biotechnol, 2018, 6(89.

[62] Zhang Y, et al. m6A modification in RNA: biogenesis, functions and roles in gliomas. J Exp Clin Cancer Res, 2020, 39(1): 192.

[63] Zhang L, et al. The role of N(6)-methyladenosine (m(6)A) modification in the regulation of circRNAs. Mol Cancer, 2020, 19(1): 105.

[64] Yi YC, et al. Novel insights into the interplay between m(6)A modification and noncoding RNAs in cancer. Mol Cancer, 2020, 19(1): 121.

[65] Zhang C, et al. Reduced m6A modification predicts malignant phenotypes and augmented Wnt/PI3K-Akt signaling in gastric cancer. Cancer Med, 2019, 8(10): 4766-4781.

[66] Li P, et al. Identification and Characterization of N6-Methyladenosine CircRNAs and Methyltransferases in the Lens Epithelium Cells From Age-Related Cataract. Invest Ophthalmol Vis Sci, 2020, 61(10): 13.

[67] Sun HD, et al. Down-regulation of circPVRL3 promotes the proliferation and migration of gastric cancer cells. Sci Rep, 2018, 8(1): 10111.

[68] Tang M and Lv Y. The Role of N(6)-Methyladenosine Modified Circular RNA in Pathophysiological Processes. Int J Biol Sci, 2021, 17(9): 2262-2277.

[69] Jiang L, et al. Exosomes in Pathogenesis, Diagnosis, and Treatment of Alzheimer's Disease. Med Sci Monit, 2019, 25(3329-3335.

[70] O'brien RJ and Wong PC. Amyloid precursor protein processing and Alzheimer's disease. Annu Rev Neurosci, 2011, 34(185-204.

[71] Chen GF, et al. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacol Sin, 2017, 38(9): 1205-1235.

[72] Guo T, Noble W, and Hanger DP. Roles of tau protein in health and disease. Acta Neuropathol, 2017, 133(5): 665-704.

[73] Deture MA and Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegen, 2019, 14(1): 32.

[74] Hanslik KL and Ulland TK. The Role of Microglia and the Nlrp3 Inflammasome in Alzheimer's Disease. Front Neurol, 2020, 11(570711.

[75] Cieslik M, et al. Alterations of Transcription of Genes Coding Anti-oxidative and Mitochondria-Related Proteins in Amyloid beta Toxicity: Relevance to Alzheimer's Disease. Mol Neurobiol, 2020, 57(3): 1374-1388.

[76] Idda ML, et al. Noncoding RNAs in Alzheimer's disease. Wiley Interdiscip Rev RNA, 2018, 9(2):

[77] Lu Y, Tan L, and Wang X. Circular HDAC9/microRNA-138/Sirtuin-1 Pathway Mediates Synaptic and Amyloid Precursor Protein Processing Deficits in Alzheimer's Disease. Neurosci Bull, 2019, 35(5): 877-888.

[78] Shi Z, et al. The circular RNA ciRS-7 promotes APP and BACE1 degradation in an NF-kappaB-dependent manner. FEBS J, 2017, 284(7): 1096-1109.

[79] Mo D, et al. Circular RNA Encoded Amyloid Beta peptides-A Novel Putative Player in Alzheimer's Disease. Cells, 2020, 9(10):

[80] Zhang S, et al. Characterization of circRNA-Associated-ceRNA Networks in a Senescence-Accelerated Mouse Prone 8 Brain. Mol Ther, 2017, 25(9): 2053-2061.

[81] Sung PS, et al. Neuroinflammation and Neurogenesis in Alzheimer's Disease and Potential Therapeutic Approaches. Int J Mol Sci, 2020, 21(3):

[82] Sanchez-Sarasua S, et al. Can We Treat Neuroinflammation in Alzheimer's Disease? Int J Mol Sci, 2020, 21(22):

[83] Lian H, et al. Astrocyte-Microglia Cross Talk through Complement Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer's Disease. J Neurosci, 2016, 36(2): 577-589.

[84] Hampel H, et al. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer's Disease. Front Immunol, 2020, 11(456.

[85] Su F, Bai F, and Zhang Z. Inflammatory Cytokines and Alzheimer's Disease: A Review from the Perspective of Genetic Polymorphisms. Neurosci Bull, 2016, 32(5): 469-480.

[86] Wang H, et al. Circular RNA circPTK2 regulates oxygen-glucose deprivation-activated microglia-induced hippocampal neuronal apoptosis via miR-29b-SOCS-1-JAK2/STAT3-IL-1beta signaling. Int J Biol Macromol, 2019, 129(488-496.

[87] Yang H, et al. Circular RNA circ_0000950 promotes neuron apoptosis, suppresses neurite outgrowth and elevates inflammatory cytokines levels via directly sponging miR-103 in Alzheimer's disease. Cell Cycle, 2019, 18(18): 2197-2214.

[88] Butterfield DA and Lauderback CM. Lipid peroxidation and protein oxidation in Alzheimer's disease brain: potential causes and consequences involving amyloid beta-peptide-associated free radical oxidative stress. Free Radic Biol Med, 2002, 32(11): 1050-1060.

[89] Butterfield DA. The 2013 SFRBM discovery award: selected discoveries from the butterfield laboratory of oxidative stress and its sequela in brain in cognitive disorders exemplified by Alzheimer disease and chemotherapy induced cognitive impairment. Free Radic Biol Med, 2014, 74(157-174.

[90] Tapia-Rojas C, et al. It's all about tau. Prog Neurobiol, 2019, 175(54-76.

[91] Cheignon C, et al. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol, 2018, 14(450-464.

[92] Huang JL, et al. Neuroprotective Properties of Panax notoginseng Saponins via Preventing Oxidative Stress Injury in SAMP8 Mice. Evid Based Complement Alternat Med, 2017, 2017(8713561.

[93] Huang JL, et al. Identification of Differentially Expressed Profiles of Alzheimer's Disease Associated Circular RNAs in a Panax Notoginseng Saponins-Treated Alzheimer's Disease Mouse Model. Comput Struct Biotechnol J, 2018, 16(523-531.

[94] Zhu R, et al. The silent information regulator 1 pathway attenuates ROS-induced oxidative stress in Alzheimer's disease. J Integr Neurosci, 2020, 19(2): 321-332.

[95] Reddy PH and Oliver DM. Amyloid Beta and Phosphorylated Tau-Induced Defective Autophagy and Mitophagy in Alzheimer's Disease. Cells, 2019, 8(5):

[96] Zhang Y, et al. The Role of Non-coding RNAs in Alzheimer's Disease: From Regulated Mechanism to Therapeutic Targets and Diagnostic Biomarkers. Front Aging Neurosci, 2021, 13(654978.

[97] Diling C, et al. Circular RNA NF1-419 enhances autophagy to ameliorate senile dementia by binding Dynamin-1 and Adaptor protein 2 B1 in AD-like mice. Aging (Albany NY), 2019, 11(24): 12002-12031.

[98] Huang JL, et al. Comprehensive analysis of differentially expressed profiles of Alzheimer's disease associated circular RNAs in an Alzheimer's disease mouse model. Aging (Albany NY), 2018, 10(2): 253-265.

[99] Cui W, et al. Inhibition of PTEN Attenuates Endoplasmic Reticulum Stress and Apoptosis via Activation of PI3K/AKT Pathway in Alzheimer's Disease. Neurochem Res, 2017, 42(11): 3052-3060.

[100] Sheng R, et al. Circular RNAs and their emerging roles as diagnostic and prognostic biomarkers in ovarian cancer. Cancer Lett, 2020, 473(139-147.

[101] Dube U, et al. An atlas of cortical circular RNA expression in Alzheimer disease brains demonstrates clinical and pathological associations. Nat Neurosci, 2019, 22(11): 1903-1912.

[102] Lo I, et al. Linking the association between circRNAs and Alzheimer's disease progression by multi-tissue circular RNA characterization. RNA Biol, 2020, 17(12): 1789-1797.

[103] Liu L, et al. Identification of Circular RNA hsa_Circ_0003391 in Peripheral Blood Is Potentially Associated With Alzheimer's Disease. Front Aging Neurosci, 2020, 12(601965.

[104] Li Y, et al. Circular RNA expression profile of Alzheimer's disease and its clinical significance as biomarkers for the disease risk and progression. Int J Biochem Cell Biol, 2020, 123(105747.

[105] Li S, et al. Screening for functional circular RNAs using the CRISPR-Cas13 system. Nat Methods, 2021, 18(1): 51-59.

[106] Ickenstein LM and Garidel P. Lipid-based nanoparticle formulations for small molecules and RNA drugs. Expert Opin Drug Deliv, 2019, 16(11): 1205-1226.

[107] Lavenniah A, et al. Engineered Circular RNA Sponges Act as miRNA Inhibitors to Attenuate Pressure Overload-Induced Cardiac Hypertrophy. Mol Ther, 2020, 28(6): 1506-1517.