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Review

Circular RNAs in depression: Biogenesis, function, expression, and therapeutic potential

Hua Gan [a,1], Yuhe Lei [b,1], Naijun Yuan [a], Kairui Tang [a], Wenzhi Hao [a], Qingyu Ma [a], Mansi Wu [a], Xuan Zhou [a], Xiaojuan Li [a], Junqing Huang [a], Lijuan Deng [a,*], Jiaxu Chen [a,*]

[a] Formula-Pattern Research Center, School of Traditional Chinese Medicine, Jinan University, Guangzhou, 510632, China
[b] Department of Pharmacy, Shenzhen Hospital of Guangzhou University of Chinese Medicine, Shenzhen, 518034, China

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ABSTRACT

Depression is the second most common disease burden worldwide that threatens human health; however, mechanisms underlying the development of depression remain unclear. A family of non-coding RNAs, circular RNAs (circRNAs), has been shown to play a critical role in the development of depression by competitively binding to certain microRNAs (miRNA) and regulating the expression of target genes. Behavioral symptoms of depression may be ameliorated by knockdown or overexpression of depression-associated circRNAs. In this review, we summarized important functions of circRNAs and analyzed the most recent findings regarding the expression and biological function of circRNAs in depression. We discussed novel circRNA-based strategies to illuminate potential therapeutic targets that may aid in the development of new treatments for depression.

1. Introduction

Depression, also known as major depressive disorder or clinical depression, is a leading cause of morbidity and mortality worldwide, with approximately 340 million people suffering from it and up to 1 million people dying each year due to depression-induced suicide [1]. Depression is a common mental health disorder which is characterized by various emotional and physical problems including depressed mood, inability to feel pleasure, low self-esteem, excessive guilt, suicidal ideation, changes in appetite and sleep, psychomotor retardation, poor concentration, and fatigue [2]. The pathogenesis of depression involves a range of factors including genetics, biochemistry, immunology, neuroendocrinology, electrophysiology, neurological structure, psychosocial factors, and epigenetic regulation [3]. In particular, the exposure to maltreatment and neglect as a child may enhance the likelihood to develop depression [4]. The extreme sensory processing patterns may contribute to the complex pathophysiology of depression and unfavorable outcomes [5]. Additionally, a growing body of researches indicated that imbalanced and abnormal internal linkage of nervous system, immune system, and endocrine system form a complex network

Abbreviations: circRNAs, circular RNAs; miRNA, microRNAs; HPA, hypothalamus pituitary adrenal; ncRNA, non-coding RNA; lncRNAs, long non-coding RNAs; ceRNA, competitive endogenous RNA; MDD, Major depressive disorder; CUS, chronic unpredictable stress; CUMS, chronic unpredictable mild stress; LPS, lipopolysaccharide; MS, maternal separation; ciRNAs, circular intronic RNAs; EIciRNAs, exon-intron circRNAs; RBPs, RNA-binding proteins; MREs, miRNA response elements; CDR1as, cerebellar degeneration-related protein 1 antisense; 3′-UTR, 3′-untranslated region; ciRS-7, circular RNA sponge for miR-7; AKT3, AKT serine/threonine kinase 3; CDK2, cyclin-dependent kinase 2; ID1, anti-senescence protein inhibitor of differentiation or DNA binding protein; E2F1, E2F transcription factor 1; FAK, focal adhesion kinase; HIFα, hypoxia-inducible factor α; MBL, muscleblind; snRNAs, small nuclear RNAs; Pol II, RNA polymerase II; AD, Alzheimer's disease; PD, Parkinson's disease; SZ, schizophrenia; MPP, 1-Methyl-4-Phenyl-Pyridinium; AGO, argonaute; NF-κB, nuclear factor-Kb; DLPFC, dorsolateral prefrontal cortex; PBMCs, peripheral blood mononuclear cells; PFC, prefrontal cortex; qRT-PCR, quantitative Real-time Polymerase Chain Reaction; QSBSS, Qi stagnation and blood stasis syndrome; HSP90, heat shock protein 90; ALKBH5, human AlkB homolog 5; T2DM, type-2 diabetes mellitus; EA, electroacupuncture; SLPNs, saponins isolated from the leaves of Panax notoginseng; VMPC, ventral medial prefrontal cortex; CREB1, cyclic-AMP response element binding protein 1; BNDF, brain derived neurotrophic factor; rTMS, repetitive transcranial magnetic stimulation; CNS, central nervous system; FMT, fecal microbiota transplantation; NLRP3 KO, pyrin domain containing protein 3 knock out; PPP1R13B, protein phosphatase 1 regulatory subunit 13B; ERS, endoplasmic reticulum stress; FAAH, fatty acid amide hydrolase.

* Corresponding authors.
E-mail addresses: ljdeng@jnu.edu.cn (L. Deng), chenjiaxu@hotmail.com (J. Chen).
[1] These authors made equal contributions.

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through neurotransmitters, cytokines, and endocrine hormones, resulting in the onset and progression of depression [6–8]. However, the pathogenesis of depression has not been clearly defined.

Epigenetic regulatory mechanisms such as non-coding RNA (ncRNA) regulation, DNA methylation, histone modification, and chromatin remodeling are known to be associated with depression [9–11]. CircRNAs, a class of ncRNAs, are attracting increasing attention [12]. Unlike mRNA, circRNAs form a covalently closed loop without the 5′-cap structure and the 3′-poly-A tail [13]. Similar to competitive endogenous RNA (ceRNA), circRNAs act as sponges to bind and inhibit the activity of miRNAs [14], thus regulating the expression of target genes at the transcriptional and post-transcriptional levels through destabilization and translational silencing of mRNAs [15].

Accumulating evidence suggests that circRNAs are involved in many major diseases, including depression [16], cancer [17,18], cardiovascular disease [19], and innate immune response [20]. The participation of circRNAs in pathogenesis of depression has attracted considerable attention because aberrant expressions of circRNAs have been found through transcriptome analyses in the peripheral blood of humans and animal models with depression. Likewise, the role of circRNAs as novel therapeutic targets to ameliorate depression-like symptoms has been demonstrated in various animal models [21–24]. In this study, through literature retrieval in Pubmed (https://pubmed.ncbi.nlm.nih.gov/) with "circRNA", "depression", and "major depressive disorder (MDD)" as the keywords, we reviewed recent discoveries regarding the biogenesis and biological functions of circRNAs and research progress on the utility of circRNAs in treating depression.

2. Biogenesis of circRNAs

CircRNAs are an emerging class of endogenous non-coding RNAs that form covalently closed, continuous loop structures lacking 5′- and 3′-terminal ends. Originating from various genomic regions, circRNAs are synthesized by the back-splicing of protein-coding precursor mRNAs (primarily in eukaryotes) [25,26]. Since discovered about four decades ago, more than 10,000 circRNAs have been identified in organisms such as worms, fruit flies, mice, monkeys, and humans [27–35], as well as in plants, fungi, and protists [13,36–38]. Researchers have revealed that

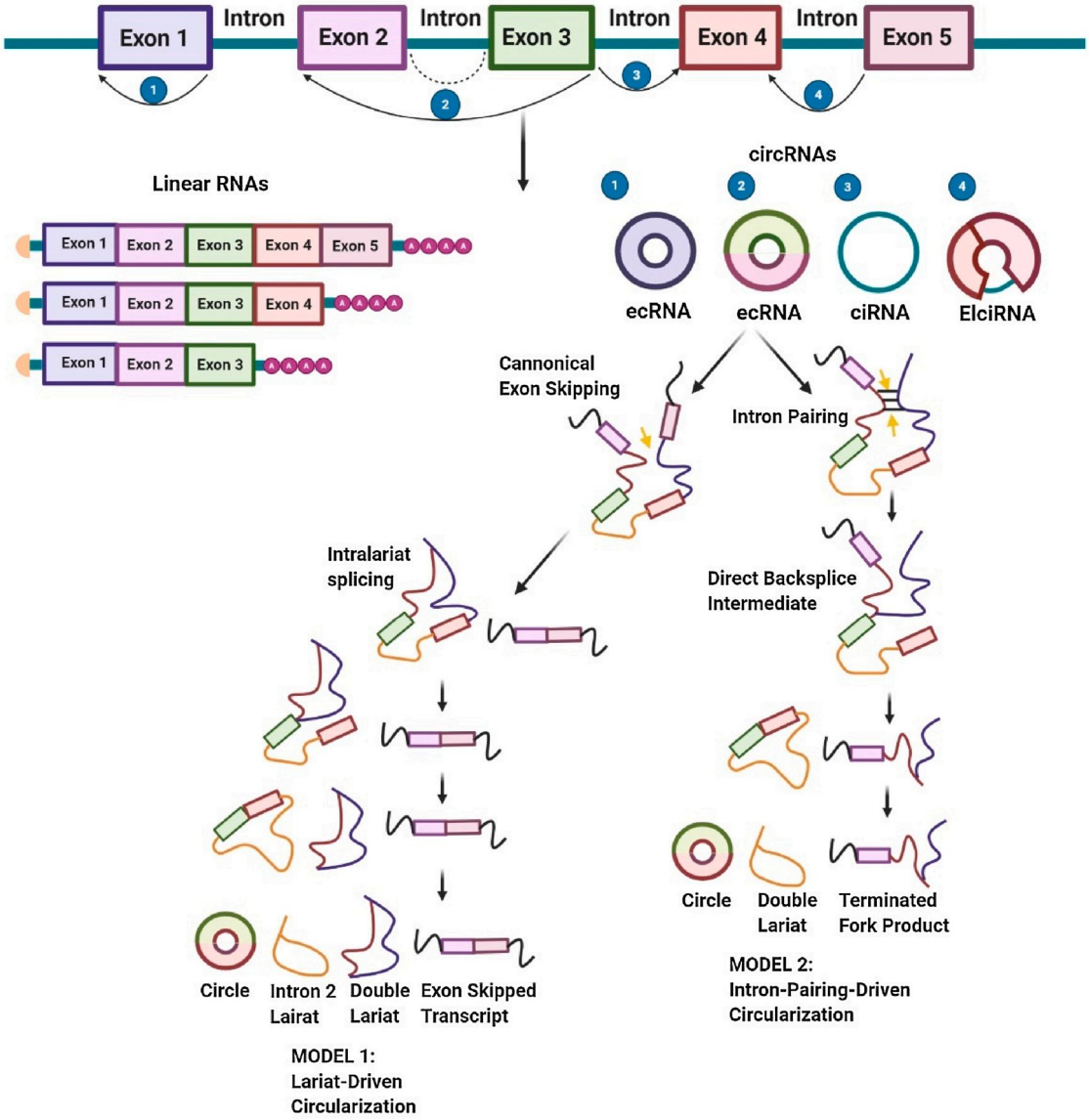

Fig. 1. CircRNA types and mechanisms of formation for two exonic circular RNAs (ecRNAs). A pre-mRNA produces various linear RNAs and circRNAs. In circRNAs, ecRNAs are spliced to contain exon(s) alone, while circular intronic (ciRNAs) are composed of introns only, and EIciRNAs contain both introns and exons. In model 1, exon-containing lariats are internally spliced into an exon circle through exon-skipping. Circularization of the lariat in model 2 is independent of exon-skipping events; nonsequential donor-acceptor pairs into apposition by ALU complementarity or other RNA secondary structures.

most circRNAs are formed from exons [39], implicating that they may play a role in gene regulation and expression.

Three types of circRNAs have been reported, which are produced via different molecular processes, including circular intronic RNAs (ciRNAs), retained-intron or exon-intron circRNAs (EIciRNAs), and intergenic circRNAs [40,41] (Fig. 1). Two different models of circRNA formation have been proposed: an exon-skipping process known as "Lariat-Driven Circularization" and a nonsequential donor-acceptor pairing process called "Intron-Pairing-Driven Circularization" or "direct back splicing" [28]. In the Lariat-Driven Circularization model, canonical splicing generates a linear RNA with missing exons contained within a lariat. Removal of the lariat and back-splicing then produce circRNAs. In the Intron-Pairing-Driven Circularization model, back-splicing generates a circRNA molecule and an exon-intron(s)-exon intermediate, which is then processed into a linear RNA with skipped exons [42,43].

Independent of the mechanism of synthesis, circRNAs participate in the development of diseases by regulating gene expression at several levels, such as regulating mRNA splicing and transcription, interacting with RNA-binding proteins (RBPs), and acting as miRNA sponges [14]. CircRNAs have been reported to affect cell autophagy, apoptosis, cell proliferation, aging, and cancer regulation in numerous ways [44–46]. CircRNAs are abundantly expressed in the brain and are highly active at neuronal synapses [21,28,47–50], suggesting that circRNAs play prominent roles in brain health and neurological diseases, including neuropsychiatric disorders.

3. Functional implications of circRNAs

As a novel class of endogenous noncoding RNAs, circRNAs play numerous roles in maintaining normal reproductive development and aging, and may influence disease development. CircRNAs may act as miRNA sponges by interacting with RBPs, and regulating mRNA transcription, splicing, and translation [14,41,51]. Recent studies have shown that circRNAs are pseudogenes that can be translated into peptides [52–56] (Fig. 2).

3.1. Inhibition of miRNA function

MiRNAs negatively regulate gene expression by inhibiting mRNA translation or by facilitating mRNA degradation [57]. MiRNAs affect the stability of an mRNA target by complementary base pairing with the 3′-untranslated region (3′-UTR) of the mRNA and modulating gene expression in the nucleus and cytoplasm [58,59]. CeRNAs compete with miRNAs for miRNA response elements (MREs) and affect the activity of miRNA molecules on target mRNAs [58,60]. Recently, a circRNA was confirmed to be a variant of a ceRNA, which competitively paired with an MRE to exert a post-transcriptional regulatory effect on the target mRNAs [61]. Hansen et al. have shown that the human cerebellar degeneration-related protein 1 antisense (CDR1as) circRNA acts as a miR-7 sponge and named this circular transcript circular RNA sponge for miR-7 (ciRS-7). CiRS-7 contains more than 70 selectively conserved miRNA target sites [14]. CiRS-7 is abundantly expressed in the mammalian brain [49,62], where it increases the translation of the miR-7 target mRNA [14,49]. Similarly, circular ZNF609 (cirZNF609) functions as a sponge to regulate the expression of the miR-150-5p target molecule AKT serine/threonine kinase 3 (AKT3) [63]. Moreover, studies have shown that circular Foxo3 (circFoxo3) [15], mm9_circ_012559 [64], and circRNAs from the human C_2H_2 zinc finger gene family also function as miRNA sponges [30]. Although a large number of studies have reported that circRNAs function as molecular sponges, it is not known whether miRNAs sponged by circRNAs affect the development and progression of neurological diseases, especially emotional diseases such as depression.

3.2. Interactions with proteins and RBPs

CircRNAs directly bind to target proteins to regulate protein function. CircFoxo3 produces anti-proliferative effects and blocks cell cycle progression by weakening the activity of cyclin-dependent kinase 2 (CDK2) through formation of the circFoxo3-p21-CDK2 ternary complex [15]. Ectopic expression of circFoxo3 has been observed to induce cellular senescence by preventing nuclear translocation of the following proteins: anti-senescence protein inhibitor of differentiation or DNA binding protein (ID1), E2F transcription factor 1 (E2F1), anti-stress protein known as focal adhesion kinase (FAK), and hypoxia-inducible factor α (HIFα). CircRNAs may bind to RBPs to regulate the splicing of mRNAs. Circular MBL (circMBL) contains conserved muscleblind (MBL/MBNL1) RNA binding sites, which are derived from the second exon of the MBL mRNA. The specific binding of circMBL to MBL mRNA

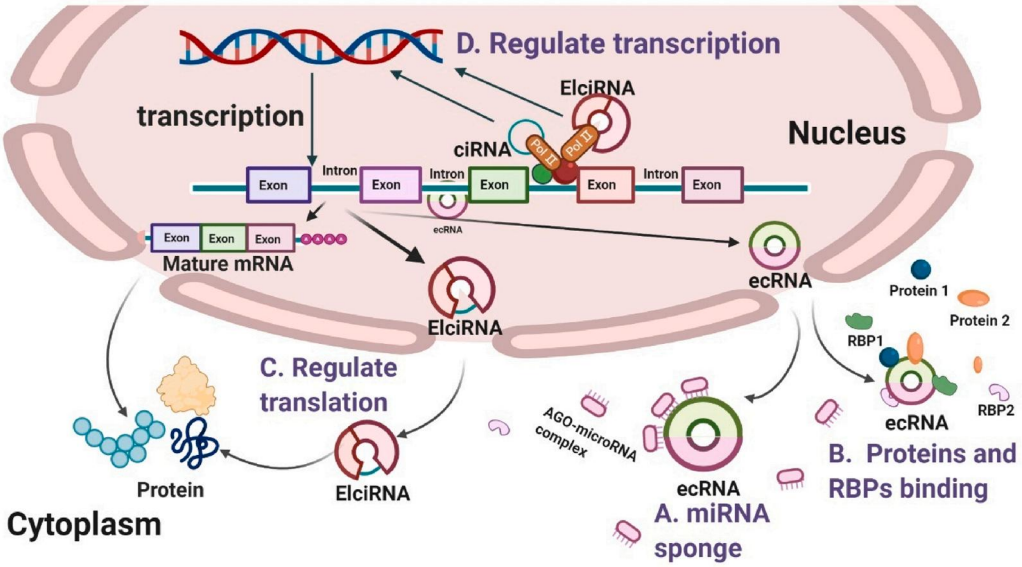

Fig. 2. Schematic representation of circRNA molecular functions. (A) CircRNAs act as miRNA sponges by interacting with AGO proteins and binding to miRNA response elements, thereby competing with miRNAs to modulate gene expression. (B) CircRNAs also may bind to RBPs and some proteins. (C) Some circRNAs may be translated to form functional proteins. (D) CircRNAs regulate transcription by interacting with RNA Pol II and influencing the expression of their parental genes.

regulates gene expression by inhibiting the linear splicing of the MBL mRNA [65]. Additionally, circular PABPN1 (circPABPN1) has been reported to inhibit linear splicing by binding to the HuR protein to reduce HeLa cell proliferation and PABPN1 translation [66]. Regardless of inhibiting cell proliferation or blocking the cell cycle, circRNAs appear to play a vital role in the pathogenesis of mental diseases, which may make circRNAs a potential target of therapeutic drugs for mental diseases.

3.3. Transcription and translation

CircRNAs are believed to regulate gene transcription. EIciRNAs (a subclass of circRNAs) have been shown to promote gene transcription through interactions with U1 small nuclear RNAs (snRNAs) and RNA polymerase II (Pol II) [41]. Processing of linear mRNAs competes with the processing of circRNAs, resulting in a negative correlation between the splicing efficiency of certain genes and the generation of circRNAs [65]. Emerging evidence indicates that a small number of circRNAs can be translated despite lacking both terminal 5′ and 3′ ends [53,55,56].

4. CircRNAs and depression

4.1. CircRNAs, brain development, and neurological disorders

CircRNAs maintain specificity and conservatism in the process of dynamic expression and are highly enriched in the mammalian brain, independent of linear transcripts [62]. A study by Rybak et al. demonstrated that more than half of 15,849 mouse circRNAs, which are highly abundant, conserved, and dynamically expressed in the brain, are upregulated during the maturation of neurons [62,65]. Many circRNAs appear to be particularly enriched in the cerebellum, a brain area rich in neuronal spines, synapses, and neurons, indicating possible involvement of circRNAs in the regulation of the nervous system. Compared with other cytoplasmic RNAs, circRNAs seem to be more prone to being localized in synapses and their expression is correlated with neural plasticity, which further supports an important function of circRNAs in synaptic transmission [50,62].

CircRNAs are believed to play essential roles in neurological disorders because they back-splice from neural genes and many circRNAs originate from genes with pivotal regulatory functions in neurons and in brain development [67]. The links between circRNAs and neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, and schizophrenia (SZ) have been widely confirmed. For example, miR-7 is expressed in tyrosine hydroxylase-positive nigral neurons in mice and humans. MiR-7 targets the PD-related α-synuclein protein [68] and protects dopaminergic SH-SY5Y cells, as well as neural progenitor cells derived from the ReNcell VM cell line, from 1-Methyl-4-Phenyl-Pyridinium (MPP(+))-induced toxicity. The protective effect of miR-7 occurs by relieving nuclear factor-κB (NF-κB) suppression and by reducing RelA protein expression [69]. Interestingly, the circRNA of human CDR1as/ciRS-7 is a miR-7 sponge, which harbors 74 binding sites for miR-7 and is able to bind to the argonaute (AGO) protein in a miR-7-dependent manner. Binding to the AGO protein allows the circRNA of human CDR1as/ciRS-7 to participate in the initiation and progression of PD [14,70].

In an animal model where the CR1as locus was removed from the mouse genome, CDR1as-deficient mice displayed a strongly impaired sensorimotor gating deficiency in which the animals were unable to filter out unnecessary information. A similar deficiency has been associated with neuropsychiatric disorders in humans [49]. In addition, dysregulation of ciRS-7 has been found in zebrafish with an impaired midbrain [71] and in the hippocampus of AD patients [45]. Expression profiles of circRNAs were analyzed by enrichment sequencing in cerebral cortex (BA46) samples collected from 35 postmortem patients with SZ and from healthy controls. Significant diversity for over 90,000 circRNAs was detected in the human dorsolateral prefrontal cortex (DLPFC) [72]. These studies suggest that circRNAs participate in the pathogenesis of multiple neurological disorders.

4.2. Basic research progress and expression of circRNAs in depression

Depression is a neurological disorder known to be affected by circRNAs through post-transcriptional regulation [73–76]. To study this issue, various animal models with depression have been established including the chronic unpredictable stress (CUS) model, chronic unpredictable mild stress (CUMS) model, lipopolysaccharide (LPS) model, and maternal separation (MS) model. Transcriptome analysis is a newly emerging method of high-throughput sequencing that has shown considerable promise for studying the role of circRNAs in the occurrence and development of depression. Transcriptome analysis has been used to identify thousands of circRNAs that are expressed in peripheral blood mononuclear cells (PBMCs), and has shown that circRNAs are expressed at significantly higher levels than corresponding linear mRNAs [33]. Also, prefrontal cortex (PFC) and hippocampus tissues are commonly used in the analysis of differentially expressed circRNAs. Cui et al. identified four differentially expressed circRNAs, namely hsa_circRNA_002143, hsa_circRNA_103636, hsa_circRNA_100679, and hsa_circRNA_104953, between depression patients and controls using quantitative Real-time Polymerase Chain Reaction (qRT-PCR) and a human circRNA array, which included 13,617 human circRNAs [77]. In an exploration of depression caused by conditions known as Qi stagnation and blood stasis syndrome (QSBSS) in traditional Chinese medicine, next-generation sequencing identified 2 circRNAs that were differentially expressed, indicating a possible biological function of circRNAs in the pathogenesis of QSBSS-induced depression [78]. A study by Zheng et al. identified 20 circRNAs that were significantly over-expressed, and 17 circRNAs that were significantly under-expressed, in the PFC of MS rats compared with a control group [79]. These results suggest that circRNAs play an important role in depression; however, whether depression leads to the differential expression of circRNAs or changes in circRNA expression cause abnormal behavior requires further investigation. Additional details about the expression of circRNAs in depression, such as the organisms and tissues that have been studied, are summarized in Table 1.

Accumulating evidence has shown how circRNAs, important components of the nervous system, are involved in the onset and development of depression (Fig. 3). Researchers have reported that the level of circular DYM (circDYM) was significantly lower in the peripheral blood of patients with depression and in two depressive-like mouse models induced by CUS and LPS. The lower level of circDYM may contribute to the development of depression. Restoration of circDYM expression significantly attenuated depressive-like behaviors, which may have been mediated by circDYM acting as an endogenous miR-9 sponge to inhibit miR-9 activity, resulting in a decrease of microglial activation via heat shock protein 90 (HSP90) ubiquitination [21] (Fig. 3B). Furthermore, circular STAG1 (circSTAG1) and circular HIPK2 (circHIPK2) were reported to function in astrocyte activation. Aberrant expression of circSTAG1 and circHIPK2 has been correlated with astrocyte dysfunction, which may partially induce depressive symptoms. Knockdown of circHIPK2 and overexpression of circSTAG1 have been shown to induce an inhibitory effect on the progression of depression, due to the binding mechanism between circSTAG1 and human AlkB homolog 5 (ALKBH5) and the miR-9 sponge function of circHIPK2. These results suggest that these two circRNAs may be novel therapeutic targets for depression [16,22] (Fig. 3C & D).

A relationship between type-2 diabetes mellitus (T2DM) and depression has been previously reviewed [83]. An et al. identified 75 upregulated and 32 downregulated circRNAs in T2DM patients with depression compared with T2DM patients without depression. Circular TFRC (circTFRC) and circular TNIK (circTNIK) were significantly upregulated in the depression group, suggesting that the function of TFRC and TNIK may be related to the pathogenesis of depression [82].

Table 1
CircRNAs in depression.

No.	circRNA	Gene Symbol	Organism	Up-regulated	Down-regulated	Tissue	Ref.
1	mmu_circRNA010860	STAG1	Human & Mouse		√	Blood, Hippocampus, Plasma, Heart, Liver, Spleen, Lung, Kidney	[16]
2	mmu_circRNA002294	DOCK4	Mouse		√	Hippocampus	[16]
3	mmu_circRNA004239	KALRN	Mouse		√	Hippocampus	[16]
4	mmu_circRNA002292	DOCK4	Mouse		√	Hippocampus	[16]
5	hsa_circRNA_103636	DCUN1D4	Human		√	Blood	[77]
6	hsa_circRNA_002143	RNA5−8S5	Human	√		Blood	[77]
7	hsa_circRNA_100679	SH3PXD2A	Human		√	Blood	[77]
8	hsa_circRNA_104953	GTF3C5	Human		√	Blood	[77]
9	hsa_circRNA_103964	UBE2D2		√		Blood	[77]
10	hsa_circRNA_104121	TRAM2		√		Blood	[77]
11	hsa_circRNA_100018	GNB1			√	Blood	[77]
12	hsa_circRNA_103257	CELSR1			√	Blood	[77]
13	hsa_circRNA_104600	VDAC3			√	Blood	[77]
14	hsa_circRNA_102802	LOC541471			√	Blood	[77]
15	hsa_circRNA_003251	—	Human	√		Blood	[80]
16	hsa_circRNA_015115	—	Human	√		Blood	[80]
17	hsa_circRNA_100918	—	Human	√		Blood	[80]
18	hsa_circRNA_005019	—	Human		√	Blood	[80]
19	CircHIPK2	HIPK2	Mouse	√		Plasma, Hippocampus	[22]
20	mmu_circ_0001223	Bnc2	Mouse		√	ventral medial prefrontal cortex	[23]
21	rno_circRNA_014900	—	Rat	√		Hippocampus	[81]
22	rno_circRNA_005442	—	Rat		√	Hippocampus	[81]
23	CircDYM	DYM	Human & Mouse		√	Plasma, Hippocampus	[21]
24	chr3:195781950-195782172	TFRC	Human	√		Blood	[82]
25	hsa_circ_0002387	TNIK	Human	√		Blood	[82]

Another study by Jiang et al. also found that 183 circRNAs were upregulated and 64 circRNAs were downregulated in T2DM patients with depression compared with diabetic patients without depression. Among them, hsa_circRNA_003251 and hsa_circRNA_015115 may function as miR-761 sponges and participate in the circRNA-miRNA-mRNA network associated with depression [80].

4.3. Potential applications of circRNAs in the diagnosis and treatment of depression

The Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association and the International Classification of Diseases are globally used tools that define the epidemiology, management, and clinical presentation of depression diseases; however, the current diagnosis of depression lacks objective physiological and biochemical indicators. The clinical definition of depression is mainly based on symptomatic changes and the clinical experience of psychiatrists, which may cause misdiagnoses [84]. Although antidepressants and psychotherapy are currently the main clinical treatments for depression, patients often become drug dependent or show poor compliance because of long term continuous treatment, which are major limitations of current treatment options [85–88]. As a consequence, exploring novel diagnostic markers and molecular mechanisms of depression is urgently needed. CircRNAs may be involved in the onset and progression of depression, and thus may be potentially useful for diagnosis and treatment of depression.

Multiple types of treatment, including pharmacologic agents, electroacupuncture (EA), and other interventions, have been used successfully to produce anti-depressive effects. Molecular studies have shown that alterations in levels of various circRNAs and the sponge effect of circRNAs mediated by these treatments may play a vital role in regulating depression and suggest potential applications of circRNAs in the diagnosis and treatment of depression. For example, Cui et al. identified four circRNAs that were differentially expressed between depression patients and controls. After 4-week and 8-week antidepressant regimens such as citalopram combined with mirtazapine, only down-regulated hsa_circRNA_103636 recovered to normal levels, suggesting the potential value of hsa_circRNA_103636 in the diagnosis and treatment of depression [77]. Ketamine, a type of narcotic, has been reported to generate rapid therapeutic effects in patients with depression and in animal models [89]. In a recent study, Mao et al. further examined the potential influence of circRNAs on the antidepressant effects of ketamine by analyzing the expression profile of circRNAs in the hippocampus of rats treated with ketamine. Rno_circRNA_014900 and rno_circRNA_005442 emerged as potentially useful molecules in the treatment of stress-related depression [81]. Additionally, Zhang et al. found that saponins isolated from the leaves of *Panax notoginseng* (sanchi ginseng) (SLPNs) could ameliorate depressive-like behavior in the CUMS mouse model. CircRNA expression profiles obtained from high-through sequencing of the ventral medial prefrontal cortex (VMPC) and hippocampus tissues of mice identified a large number of differentially expressed circRNAs. Among them, mmu_circ_0001223 was significantly down-regulated in CUMS mice, but was significantly up-regulated by SLPN treatment, indicating that mmu_circ_0001223 may be an important mediator of SLPN's anti-depression effects [90]. Cyclic-AMP response element binding protein 1 (CREB1) and brain derived neurotrophic factor (BNDF)-related signaling pathways have been reported to participate in the pathogenesis of depression [91]. This study also confirmed that elevated protein levels of CREB1 and BDNF induced by SLPN may be attributed to up-regulation of mmu_circ_0001223 [90].

In addition to drugs and plant extracts, other types of interventions may also exert anti-depression effects by modulating circRNAs. Baduanjin is a traditional Chinese exercise therapy, which has been widely practiced in China for centuries [92]. Previous studies have shown that practicing Baduanjin may benefit patients with depression and anxiety [93]. An et al. investigated molecular changes that occurred during a 12-week Baduanjin intervention and identified 266 differentially expressed circRNAs (170 down-regulated and 96 up-regulated). This study provided valuable insights into potential mechanisms by which Baduanjin may ameliorate the symptoms of depression and alter blood glucose levels in depression patients [94]. Zheng et al. examined the underlying mechanisms through which EA modulates depressive behaviors. Their research identified beneficial therapeutic effects from repeated EA treatment at the acupoints Baihui (GV20) and Yintang

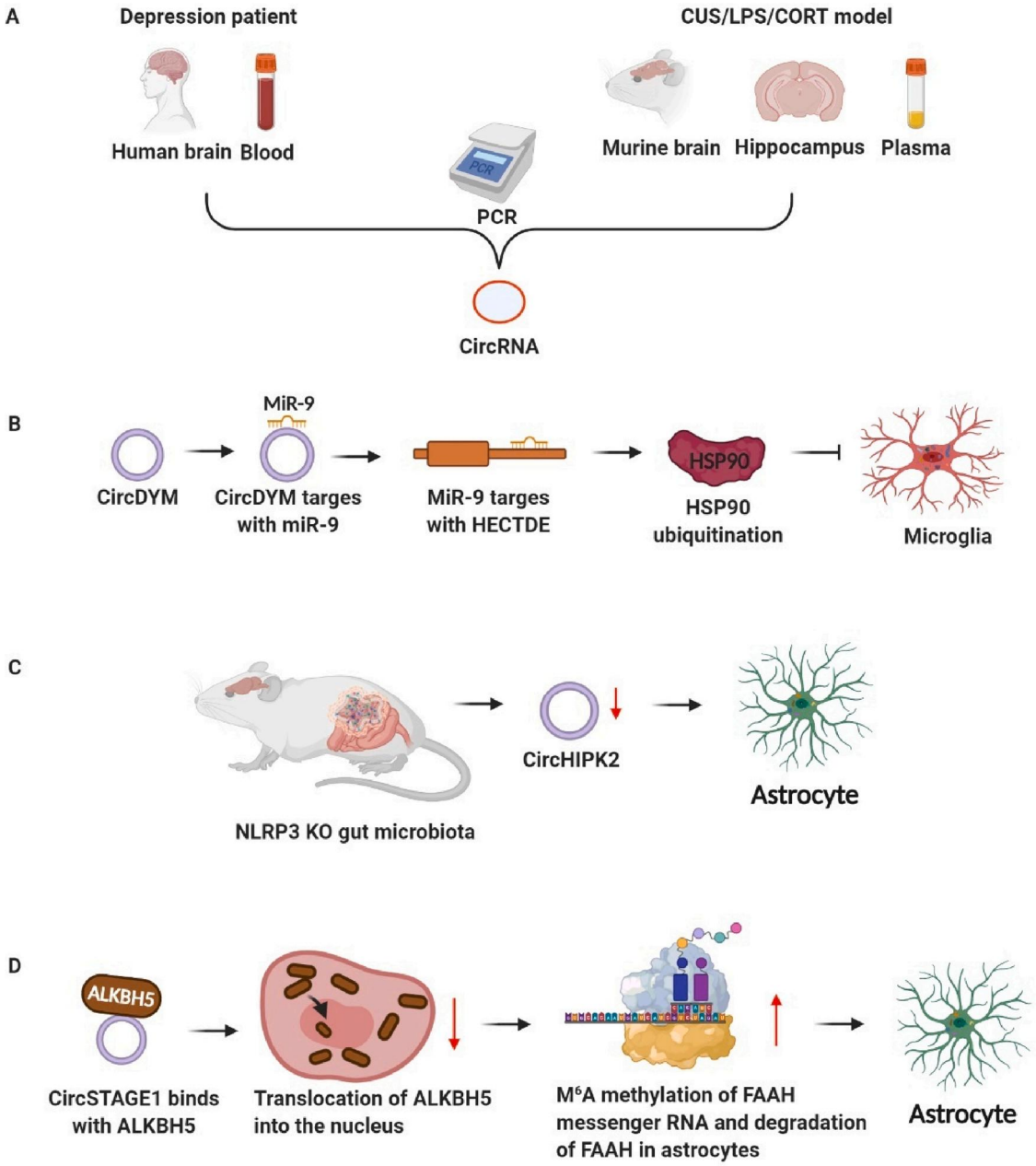

Fig. 3. The specific molecular mechanism of circRNAs in depression. (A) The qRT-PCR has been used to verify differentially expressed circRNA in human brain, blood, and murine brain, hippocampus and plasma. (B) CircDYM targets miR-9 to regulate microglial activation through HSP90 ubiquitination in the CUS/LPS model mouse. (C) Transplantation of the NLRP3 KO gut microbiota decreases the expression of circHIPK2 and reverses astrocyte dysfunction in the CUS model mouse. (D) The binding of CircSTAG1 and ALKBH5 inhibits the translocation of cytoplasmic ALKBH5 into the nucleus, and promotes the up-regulation of m^6A methylation of fatty acid amide hydrolase (FAAH) messenger RNA. This process increases degradation of FAAH in astrocytes, and finally attenuates astrocyte dysfunction induced by CUS and corticosterone.

(GV29) in patients with depression-like behavioral deficits. Unbiased genome-wide RNA sequencing was used to identify differentially expressed circRNAs in the PFC of depression rats that resulted from EA treatment. Two circRNAs that showed increased expression in depression rats compared with EA rats, and one circRNA that showed decreased expression in the depression group compared with the EA group, were identified. These three circRNAs, derived from *LOC102555866*, *Npepo*, and *Cdh12*, may play an important role in ameliorating depression-related manifestations by EA at GV20 and GV29 [79]. As mentioned above, restoration of circDYM expression significantly ameliorates depressive-like behavior. Therefore, visual cortical repetitive transcranial magnetic stimulation (rTMS), a noninvasive intervention in depression, may up-regulate circDYM expression to produce anti-depressive effects, further confirming the significant role of circDYM as a biomarker for the diagnosis and treatment of depression [95].

Recent studies have identified a correlation between the gut microbiota and depression. It is widely accepted that the alteration of composition of bacterial communities in the gut caused by different stress have the potential to affect various metabolic pathways which may be involved in the development of depressive states [96,97]. The participation of gut microbiome in bidirectional communication pathway with the central nervous system (CNS) was named the microbiota–gut–brain axis, which is believed to regulate various central processes through microbial metabolites [98]. To identify potential biomarkers of depression in correlation with the metabolism of the gut

microbiota may enhance the diagnostic criteria for depression [99]. In addition, fecal microbiota transplantation (FMT) has been reported to have therapeutic effects on depression [100]. Zhang et al. investigated the underlying mechanisms that ameliorate depressive-like behaviors in mouse models that received gut microbiota transplantation. This study found that the expression level of circHIPK2 increased significantly in a CUS mouse model with depression compared with a control group. Transplantation of the gut microbiota from pyrin domain containing protein 3 knock out (NLRP3 KO) mice alleviated astrocyte dysfunction in CUS mice. Improved astrocyte function was attributed to the regulation of circHIPK2 expression. This study revealed a regulatory effect of the gut microbiota-circHIPK2-astrocyte axis in depression, and suggested that transplantation of the gut microbiota may constitute a novel therapeutic strategy for depression [22].

Although the role of circRNAs in depression is not completely understood, emerging research has confirmed the association between circRNAs and depression, making circRNAs a promising new area in antidepressant therapy.

5. Future perspectives

A series of recent studies has revealed that circRNAs exert a broad-spectrum of biological activities in depression. The molecular mechanisms related to the onset and progression of depression likely involve circRNAs that function through multiple complex signal transduction pathways. Most recently, several key circRNAs have been associated with depression, such as circDYM and circHIPK2, providing translational evidence that circRNAs may represent novel therapeutic targets for depression.

Numerous studies have shown that autophagy is closely related to depression and that many antidepressants induce the autophagy pathway [101–106]. Autophagy and circRNA activity may act synergistically to modulate depression. According to recent research, protein phosphatase 1 regulatory subunit 13B (PPP1R13B) regulated by mmu_circ_012091 contributes to the proliferation and migration of lung fibroblasts that rely on endoplasmic reticulum stress (ERS) and autophagy [107]. Circular HECTD1 (CircHECTD1) and circHIPK2 activate astrocytes via autophagic processes that target miR142-TIPARP and miR124-2HG, respectively [108,109]. CircRNAs may block autophagosome formation, maturation, selection, expansion, and degradation by regulating the expression of, or the function of, autophagy-related proteins and interfering with the normal internal environment of human cells. Given the sponge function of circRNAs and direct targeting of some proteins, circRNAs may function as key regulators in these processes. Autophagy biogenesis activated by circRNAs may be targeted in future depression therapies.

As the study of this area is in its infancy, this work is limited by the paucity of literature on the corroborations between circRNA and depression. Based on all existing research, we summarized the explorations of circRNAs in patients or animal models with depression in the past 20 years, and elucidated that circRNA plays a role in the mechanism of depression, revealing it will become a potential target for the prevention and treatment of depression. However, certain limitations exist in modulating circRNA to combat depression such as safety concerns. Meanwhile, whether changes in circRNAs are specific to depressed patients remain unknown, for the level of circRNAs may be affected by various factors including age, smoking, or drug abuse [110]. In conclusion, this issue would be a fruitful area for further work predictively. We hope the readers deem this topic intriguing and pay more attention to the etiology and treatment of depression from the perspective of circRNA. We believe a greater focus on this issue could produce interesting findings in the future, which may contribute in several ways to our understanding of circRNA and depression.

Authors' contributions

JXC and LJD designed the study and revised the manuscript. HG and YHL conducted the literature search and drafted the manuscript. NJY, KRT, and WZH were involved in the conception of the study and prepared the figures. QYM, MSW, XZ, XJL, and JQH made critical revisions to the manuscript. All authors have read and approved the final version of the manuscript.

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Declaration of Competing Interest

The authors report no declarations of interest.

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