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Non-coding RNAs in depression: Promising diagnostic and therapeutic biomarkers

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ABSTRACT

Non-coding RNAs (ncRNAs), including microRNAs, circular RNAs, and long non-coding RNAs, are important regulators of normal biological processes and their abnormal expression may be involved in the pathogenesis of human diseases including depression. Multiple studies have demonstrated a significantly increased or reduced ncRNAs expression in depressed patients compared with healthy subjects and that antidepressant therapy can alter the aberrant expression of ncRNAs in depressed patients. Although the existing evidence is important, it is also mixed and a comprehensive review to guide an effective clinical translation is lacking. Focused on human research, this review summarizes clinical findings of ncRNAs in depression, including those in brain tissues and peripheral samples. We outlined the characteristics and functions of ncRNAs and highlighted their performance in the diagnosis and treatment of depression. Although their precise roles in depression remain uncertain, ncRNAs have shown potential value as biomarkers for diagnosis and therapy in depressed patients.

1. Introduction

Depression is the most common psychiatric disease and the leading cause of disability and suicide [1,2]. The specific pathogenesis of depression is still unknown, although some potential aetiology has been proposed and acknowledged [3-5], *e.g.,* the monoamine hypothesis, hypothalamic–pituitary–adrenal axis changes, neuro-inflammation, neuroplasticity, and epigenetics. To date, clinical manifestations are a primary reference to diagnose depression, but the complexity of its pathophysiology directly affects diagnostic accuracy [6]. Identification of effective biomarkers involved in the pathogenesis of disease contributes to correctly diagnosing depression, with high abundance, stability, and convenience as the major features for outstanding biomarkers in clinic. In addition, many depressed patients fail to respond to antidepressant treatments and blindly increasing pharmacotherapy may induce significant side effects [7,8]. Hence, the identification of objective therapeutic biomarkers is essential for the clinical treatment of depression, since they could be used as targets for drug development as well as to assess and predict the efficacy of therapeutic interventions, thus guiding individualized medicine.

Non-coding RNA (ncRNA) is a special type of RNA that is transcribed from DNA but does not encode proteins [9]. It includes microRNA (miRNA), circular RNA (circRNA), long non-coding RNA (lncRNA), and other yet-to-be-discovered small RNAs. Reported evidence has demonstrated that ncRNAs can regulate gene expression by multiple mechanisms, such as affecting the transcription or translation of messenger RNA (mRNA) or DNA/RNA methylation, and that they may substantially impact pathophysiological processes in many human disorders [10,11]. Simultaneously, these characteristics of ncRNAs also make them potential targets for treatment and drug development[12]. Therefore, gaining insight into these ncRNAs will contribute not only to understanding the biological mechanisms of disease but also to directing personalised therapies.

An extensive body of research has indicated that ncRNAs play a critical role in the pathogenesis of depression (*e.g.,* in neuroplasticity and neurogenesis), which results in relevant clinical symptoms (*e.g.,* suicidal behaviour), and are influenced by antidepressant treatments [13-16]. However, given the large number of reported ncRNA

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biomarkers, it is difficult to determine which are the most clinically translational ones. In the present review, we focus on valuable discoveries related to miRNA, circRNA, and lncRNA to briefly introduce their biogenesis and function. Additionally, our main objective was to assess the clinical value of these ncRNAs as diagnostic and therapeutic biomarkers in depression and pinpoint the most valuable ncRNA biomarkers for clinical application in patients with depression based on multifaceted evidence comprising depressive-like animal models, post-mortem brain tissue, human cerebrospinal fluid, and human peripheral blood. We hope the present review can provide a helpful insight that contributes to clinical translation of ncRNA biomarkers in depression.

2. MiRNA

2.1. MiRNA biogenesis and characteristics

MiRNAs are a class of single-stranded small ncRNAs formed of about 18-25 nucleotides, and they were firstly identified by *Reinhart et al.* by controlling the development timing in Caenorhabditis elegans [17]. Being the best-studied ncRNA, the biogenesis of miRNAs has been clearly described in previous reports [18,19]. In the nucleus, the miRNA gene are transcribed to long primary miRNA (pri-miRNA) by RNA polymerase II or III. Due to processing of the Class 2 RNase III enzyme Drosha, pri-miRNAs become small hairpin miRNA precursors (pre-miRNA) with about 60∼100 nucleotides in length and a stem-loop structure. Subsequently, pre-miRNAs are transferred into the cytoplasm by the exportin-5/RanGTP complex for further biological processing. Under the action of RNase III enzyme Dicer with TAR RNA-binding protein, pre-miRNAs are converted into double-stranded mature small RNAs. Then, one of the double strands is loaded onto Argonaute homologue proteins to generate the RNA-induced silencing complex (RISC) that fulfils the biological function of mature miRNA, while the other strand is degraded rapidly [20,21].

In addition, the ability of miRNAs to regulate gene expression is a fundamental component of complex biological processes. Since the unique sequences of RISC/miRNA complex can bind to the 3' untranslated region of targeted mRNAs, miRNAs are generally considered to cause translational repression or degradation of mRNAs and direct the post-transcriptional gene regulation [22,23]. Consequently, miRNAs play an important role in regulating development and cellular differentiation, and particularly in the brain, their expression can significantly modulate neuronal development and the intracellular pathway signalling in apoptosis [24].

Furthermore, miRNAs have the following attractive properties: (1) they are stably maintained and transported in diverse biological fluids, *e.g.,* cerebrospinal fluid and peripheral serum / plasma; (2) the method used to detect them is technically simple and inexpensive; (3) their expression is tissue- and disease-specific [25,26]. Therefore, the abnormal expression of miRNAs in the brain tissue or in biological fluids (*e.g.,* cerebrospinal fluid, peripheral blood) has potential to emerge as a valuable biomarker and to help diagnose disease and predict responses to therapeutic interventions.

2.2. MiRNAs as diagnostic biomarkers for depression

In 2010, *Xu et al.* demonstrated that miRNA polymorphisms (*i.e.,* the polymorphism ss178077483 in the miRNA-30e precursor) was correlated with depression susceptibility, which firstly linked miRNAs to the pathogenesis of depression [27]. Subsequently, *Smalheiser et al.* and *Belzeaux et al.* respectively identified differential miRNA profiles in prefrontal cortex (Brodmann Area 9) or peripheral blood samples in depressed patients compared with healthy subjects for the first time [28,29]. These findings supported that abnormal miRNA expression may contribute to distinguishing depressed patients from healthy subjects. Numerous miRNAs have been identified in depression, however, the most valuable ones are yet to be determined. Hence, it is necessary to investigate the expression of miRNAs to adequately assess the value of miRNAs for the clinical diagnosis of depression.

2.2.1. miRNAs in brain tissues

Many miRNAs are highly expressed in brain tissues and may be implicated in the pathological changes of the central nervous system (CNS) in depression. Compared with normal rats, 26 miRNAs with differential expression in prefrontal cortex were detected in chronic corticosterone-induced depressed rats, and these miRNAs regulated genes that are critical to stress response and could result in depressive-like behaviour via a hyperactive hypothalamic-pituitary-adrenal axis [30]. However, although multiple miRNAs have been identified in brain tissues from depressive-like rodent models, so far only expression of miR-124 showed a relatively consistent increase in depressed rodents compared with normal rodents among different research groups [30-35]. In addition, to obtain more direct evidence that supports miRNAs as clinical biomarkers of depression, post-mortem brain tissues, including prefrontal cortex, anterior cingulate cortex, have been used as an important resource to investigate miRNAs changes between healthy and depressed subjects. To date, approximately 50 miRNAs were reported as abnormally expressed in post-mortem brain tissues of depressed patients [28,36-49]; however, none but miR-124[38, 40, 45] was repetitively found by more than one research group, and these three studies [38,40,45] reported completely different results regarding miR-124 in depressed patients although the available evidence suggests that miR-124 may mediate the neuronal differentiation, synaptogenesis, and microglial activation by regulating target genes (Table 1). As discussed above, examining miRNA expression in the brain may contribute to elucidating the association between miRNAs and depression, but the differences in animal models and the heterogeneity of brain tissues and patient populations could lead to inconsistent results.

2.2.2. miRNAs in peripheral blood

For routine examination and clinical screening of depressed patients, peripheral blood is a more convenient and non-invasive source than brain tissues. Recently, *Zhang et al.* [50] found that plasma miR-134 levels, which may be related to synaptic transmission and plasticity [51], were significantly downregulated in depressed patients. In agreement with this, reduced miR-134 levels were reported in plasma samples, hippocampus tissue, and prefrontal cortex tissue of chronic unpredictable mild stress (CUMS) rats [50]. These consistent findings between humans and rodents or between CNS and peripheral circulation suggested that miR-134 may serve as a potential biomarker for the diagnosis of depression [50], although this needs to be corroborated due to contradictory results reported in other studies [52,53].

To date, a large number of miRNAs has been identified in peripheral blood samples, including whole-blood, serum, plasma, peripheral blood mononuclear cells (PBMCs), and blood-derived exosome, and a part of them showed great clinical potential for depression. To achieve an effective clinical translation in the diagnosis of depression, promising peripheral blood miRNA biomarkers should have the following characteristics: (1) significant differential expression between depressed and healthy subjects, verified by different laboratories (basic evidence); (2) consistent verification in brain tissues of depressive-like animal models (moderate evidence); (3) consistent verification in post-mortem brain tissues (strong evidence); (4) consistent verification in the human brain in vivo using molecule positron emission tomography (PET) imaging (stronger evidence); (5) brain biopsy (strongest evidence) (Fig. 1). Therefore, in the present review, 18 peripheral blood miRNAs with relatively consistent findings across studies were proposed, comprising 13 miRNAs supported by strong

Table 1
The expression of promising microRNA diagnostic biomarkers in depressed patients or depression-like animals.

microRNAs	Study	Species	Sample type	Change	Possible targets in depression
Strong evidence					
miR-124	Wang et al. [38]	Humans	Prefrontal cortex (BA44)	Decrease	Neuronal differentiation; synaptogenesis and neuronal proliferation; BDNF-TrkB signaling pathway; microglial activation; target SAT1 and SMOX genes
	Lopez et al. [45]	Humans	Prefrontal cortex (BA44)	No difference	
	Roy et al. [40]	Humans	Prefrontal cortex (BA46)	Increase	
			Serum	Increase	
	He et al. [100]	Humans	Peripheral blood mononuclear cells	Increase	
	Fang et al. [55]	Humans	Plasma	Increase	
	Wang et al. [31]	Rodents	Hippocampus	Increase	
	Pan et al. [32]	Rodents	Hippocampus	Increase and decrease with duloxetine intervention	
	Dwivedi et al. [30]	Rodents	Prefrontal cortex	Increase	
	Xu et al. [33]	Rodents	Basolateral amygdala	Increase	
	Lou et al. [101]	Rodents	Hippocampus	Decrease	
	Tang et al. [34]	Rodents	Hippocampus	Increase	
	Yang et al. [35]	Rodents	Hippocampus	Increase	
miR-139-5p	Lopez et al. [45]	Humans	Prefrontal cortex (BA44)	Increase	Neural stem cell proliferation and neuronal differentiation; target SAT1 and SMOX genes
	Wei et al. [102]	Humans	Blood-derived exosome	Increase	
		Rodents	Blood-derived exosome	Increase	
			Brain-derived exosome	Increase	
miR-221	Smalheiser et al. [39]	Humans	Prefrontal cortex (BA10)	Increase	Wnt2/CREB/BDNF axis; anti-neuroinflammatory signaling cascades via the IRF2/IFN-α pathway
	Lian et al. [57]	Humans	Cerebrospinal fluid	Increase	
		Rodents	Serum	Increase	
			Hippocampus	Increase	
	Wan et al. [36]	Humans	Cerebrospinal fluid	Increase	
			Serum	Increase	
	Kuang et al. [103]	Humans	Serum	Increase	
	Feng et al. [104]	Humans	Serum	Increase	
miR-218	Torres-Berrío et al. [37]	Humans	Prefrontal cortex (BA44)	Decrease	Target Netrin-1 guidance cue receptor DCC; regulating density of thin dendritic spines
		Rodents	Prefrontal cortex		
	Mendes-Silva et al. [105]	Humans	Plasma	Decrease	
	Torres-Berrío et al. [106]	Rodents	Medial prefrontal cortex	Decrease	
miR-17-5p	Roy et al. [107]	Humans	Locus coeruleus	Increase	Target CREB1, CHRM2, NTRK3, and SLC17A7 genes
	Camkurt et al. [108]	Humans	Plasma	Increase	
miR-335	Smalheiser et al. [28]	Humans	Prefrontal cortex (BA9)	Decrease	Target GRM4, SOX4, PTPRN2, and MERTK genes
	Li et al. [54]	Humans	Whole-blood	Decrease and increase with citalopram intervention	
miR-1202	Lopez et al. [43]	Humans	Prefrontal cortex (BA44)	Decrease	Target GRM4 gene; regulating the metabolism of glutamate
	Gheysarzadeh et al. [109]	Humans	Serum	Decrease	
miR-135a	Issler et al. [41]	Humans	Dorsal raphe / raphe magnus	Decrease	Serotonin transporter and serotonin receptor-1a transcripts
			Whole-blood	Decrease and increase with cognitive behavioral therapy	
	Gheysarzadeh et al. [109]	Humans	Serum	Decrease	
miR-184	Azevedo et al. [47]	Humans	Anterior cingulate cortex	Decrease	Target NCOR2 and PDE4B genes
	Mendes-Silva et al. [110]	Humans	Plasma	Decrease	
miR-34c-5p	Lopez et al. [45]	Humans	Prefrontal cortex (BA44)	Increase	Target SAT1, SMOX, and NOTCH1 genes
	Sun et al. [111]	Humans	Peripheral blood leukocytes	Increase	
miR-24-3p	Lopez et al. [43]	Humans	Prefrontal cortex (BA44)	Increase	MAPK/Wnt signaling pathway
	Maffioletti et al. [112]	Humans	Whole-blood	Increase	
miR-146a	Smalheiser et al. [28]	Humans	Prefrontal cortex (BA9)	Decrease	TLR4 signaling pathway
	Hung et al. [113]	Humans	Peripheral blood mononuclear cells	Decrease and increase with antidepressant intervention	
miR-425-3p	Lopez et al. [43]	Humans	Prefrontal cortex (BA44)	Increase	MAPK/Wnt signaling pathway
	Maffioletti et al. [112]	Humans	Whole-blood	Increase	
	Belzeaux et al. [29]	Humans	Peripheral blood mononuclear cells	Increase	
Moderate evidence					
miR-132	Li et al. [56]	Humans	Serum	Increase	Target MeCP2 (directly) and BDNF (indirectly) genes; activation of the actin depolymerizing protein n-cofilin via Rac1-PAK signaling; regulating spine density and size.
	Liu et al. [114]	Humans	Whole-blood	Increase	
	Fang et al. [55]	Humans	Plasma	Increase	
	Su et al. [115]	Humans	Whole-blood	Increase	
		Rodents	Hippocampus	Increase	
	Pan et al. [32]	Rodents	Hippocampus	Decrease and increase with duloxetine intervention	
miR-9	Zhang et al. [69]	Humans	Whole-blood	Increase	Target HECTD1 gene; microglial activation
	He et al. [116]	Humans	Whole-blood	Increase	
	Buran et al. [117]	Rodents	Prefrontal cortex	Increase	
miR-451a	Wan et al. [36]	Humans	Cerebrospinal fluid	Decrease	Action of ketamine
			Serum	Decrease	
	Kuang et al. [103]	Humans	Serum	Decrease and increase with paroxetine intervention	
	Camkurt et al. [108]	Humans	Plasma	Increase	
miR-34a	Azevedo et al. [47]	Humans	Anterior cingulate cortex	Decrease	Target NCOA1 and PDE4B genes
	Wan et al. [36]	Humans	Cerebrospinal fluid	Increase	
			Serum	Increase	
	Kuang et al. [103]	Humans	Serum	Increase	

(*continued*)

Table 1 (*Continued*)

microRNAs	Study	Species	Sample type	Change	Possible targets in depression
miR-16	Song et al. [118]	Humans	Cerebrospinal fluid Whole-blood	Decrease No difference	Target SERT (serotonergic transmitter system), BDNF (neurogenesis), and BCL-2 (neuron survival and apoptosis) genes
	Gheysarzadeh et al. [109]	Humans	Serum	Decrease	
	Baudry et al. [119]	Rodents	Raphe nuclei	Decrease and increase with fluoxetine intervention	
	Bai et al. [58]	Rodents	Hippocampus	Increase	

BDNF, brain-derived neurotrophic factor; TrkB, tropomysin-related kinase B; SAT1, spermidine/spermine N^1-acetyltransferase 1; SMOX, spermine oxidase; IRF2/IFN-α, Interferon regulatory factor 2/Interferon alpha; DCC, deleted in colorectal cancer; CREB1, cAMP responsive element binding protein 1; CHRM2, cholinergic receptor muscarinic 2; NTRK3; neurotrophic receptor tyrosine kinase 3; SLC17A7, solute carrier family 17 member 7; GRM4, glutamate receptor, metabotropic 4; SOX4, SRY-box transcription factor 4; PTPRN2, protein tyrosine phosphatase receptor type N2; MERTK, MER proto-oncogene, tyrosine kinase; NCOR2, nuclear receptor corepressor 2; PDE4B, phosphodiesterase 4B; NOTCH1, notch receptor 1; TLR4, Toll-like Receptor 4; MeCP2, methyl-CpG-binding protein 2; HECTD1, HECT domain E3 ubiquitin protein ligase 1; NCOA1, nuclear receptor coactivator 1; SERT, serotonin transporter; BCL-2, BCL2 apoptosis regulator.

evidence and 5 by moderate evidence (Table 1), which should be considered as promising diagnostic biomarkers of depression.

Additionally, relevant function studies further demonstrated these miRNAs may be involved in the pathogenesis of depression, including serotonergic transmission, neuroinflammation, and synaptic plasticity (Table 1). In addition, certain miRNAs act on the same target gene and exert synergetic functions in depression. For example, (1) miR-124, miR-139-5p and miR-34c-5p, targeting the spermidine/spermine N1-acetyltransferase 1 and spermine oxidase gene, regulate neuronal differentiation and proliferation [45] (2) miR-335 and miR-1202, targeting the glutamate receptor metabotropic 4 gene, regulate glutamate metabolism [44,54]; (3) miR-124, miR-221, miR-132, and miR-16, targeting brain-derived neurotrophic factor gene, regulate synaptic plasticity [55-58]; (4) miR-24-3p and miR-425-3p, targeting MAPK/Wnt-system genes, regulate MAPK and Wnt signalling pathways [43]. In sum, the above candidate miRNAs have been proved to involve in the physiopathology of depression.

2.2.3. *miRNAs with specificity for diagnosing depression*

Considering the high overlap between the pathobiology of depression and that of other psychiatric disorders, highly-specific miRNA diagnostic biomarkers for depression are more valuable in

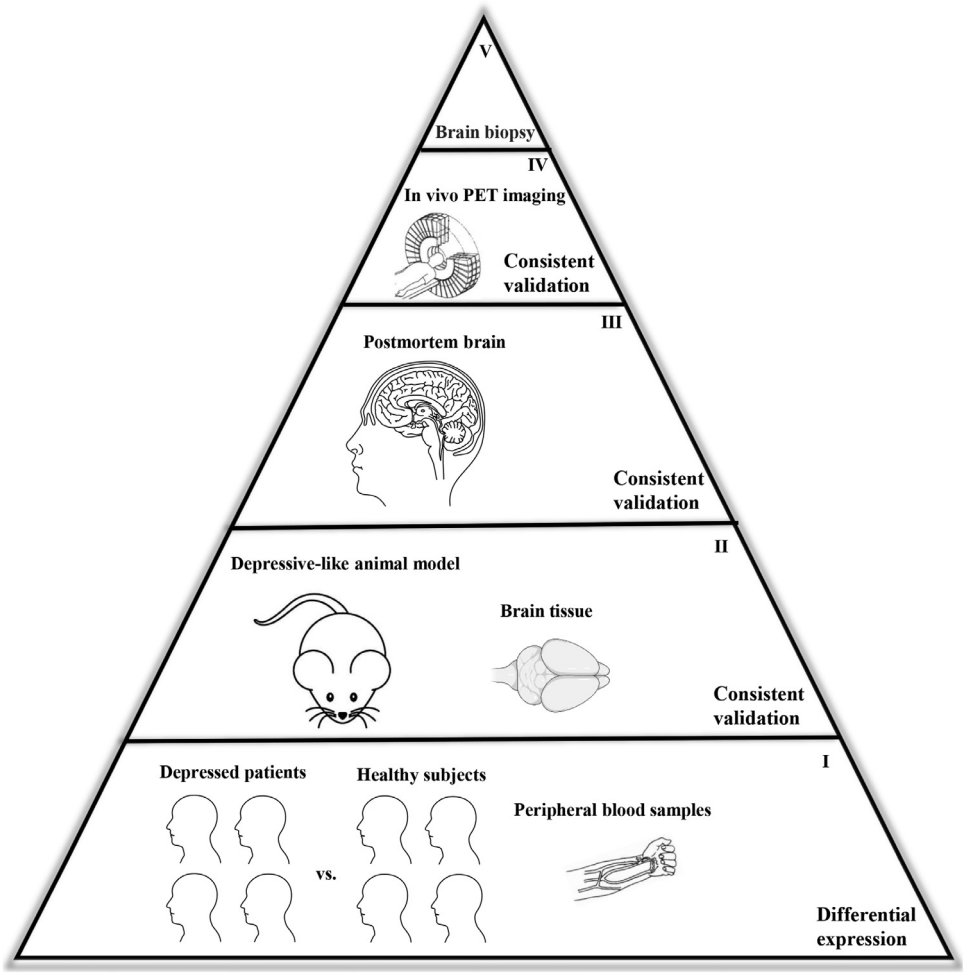

Fig. 1. The division of strength of evidence for the microRNA diagnostic biomarkers in depression I: basic evidence; I+II: moderate evidence; I+II+III: strong evidence; I+II+III+IV: stronger evidence; I+II+III+IV+V: strongest evidence PET, positron emission tomography.

clinic. Based on post-mortem brain studies, significantly decreased expression of miR-184 (*vs.* bipolar disorder) [47] and miR-152-3p (*vs.* schizophrenia or bipolar disorder) [39] was solely detected in patients with depression. Furthermore, plasma miR-134 was significantly reduced in depressed patients when compared with healthy, schizophrenic, and bipolar disorder subjects, resulting in a remarkable classification performance (accuracy $\geq$ 80%) to differentiate depressed patients from other cohorts [50]. Because these findings were only reported by one research group, multiple-centre data is critical to corroborate the potential of these miRNAs.

2.3. MiRNAs as therapeutic biomarkers for depression

In addition to helping diagnose depression, could miRNAs be influential in the clinical treatment of depression? *Bocchio-Chiavetto et al.* initially performed a direct study to assess the effects of antidepressant therapies on miRNAs in depressed patients and identified 30 miRNAs in peripheral blood whose expression changed after treatment, as well as regulated long-term potentiation and long-term depression and axon guidance [59]. Published studies suggested that the expression of several miRNAs in depressed patients can be altered by antidepressant therapies (Table 2). Among them, miR-1202 [44,60,61], miR-16 [61,62], and miR-135a [41,61] display consistent changes after treatment across different studies, making them promising candidates as therapeutic biomarkers for depression. In addition, *Fiori et al.* [61] found that, as a regulator of the glutamate metabotropic receptor 4, the baseline expression of miR-1202 in whole-blood significantly differed between responders and nonresponders, which suggested that miR-1202 could predict response to treatment in depressed patients. Furthermore, in a previous study [62], serum levels of miR-16 significantly increased in depressed patients after treatment with selective serotonin norepinephrine reuptake inhibitors, however, when selective serotonin reuptake inhibitors were administered, no significant difference in serum miR-16 expression were detected, thus suggesting that different kinds of antidepressants impact miRNA expression in a particular way and may lead to a different treatment outcome.

2.4. Brief summary

By reviewing previous studies, main findings are as follows: (1) abnormally expressed brain-derived miRNAs can play direct roles in the pathophysiology of depression and result in relevant clinical manifestations, especially suicidal behavior, however, these miRNAs can only provide valuable neuropathological clue but not be used as clinical biomarkers due to brain samples of human are difficult to obtain; (2) with the outstanding convenience, 13 peripheral miRNAs regulate target genes to affect the physiopathology of depression and exhibit consistent changes between CNS and peripheral circulation by repeatable verifications in different cohorts, therefore, these peripheral miRNAs are promising diagnostic biomarkers of depression if further evidence can clarify the original CNS source of them; (3) except for miR-184, miR-152-3p, and miR-134, more studies should be conducted to evaluate the specificity of miRNAs for depression, which are more important for the diagnosis of depression; (4) the effective antidepressant treatment can alter the pathophysiologic changes of depression and restore the aberrant expression of many miRNAs, however, only miR-1202 and miR-16 have proved to have prominent value for assessing the clinical response to antidepressant treatments, which contribute to guiding an individualized therapy to improve treatment response.

3. CircRNA

3.1. CircRNA biogenesis and function

CircRNAs are closed circular molecules generated from precursor mRNA back-splicing, which were first documented in higher plants as single-stranded circular RNA viroids. [63] CircRNAs have a unique covalently-closed loop structure formed via the joining of an upstream 3′ splice site to a downstream 5′ splice site [64]. The biogenesis of circRNAs remains unclear, although there are three main formation pathways—the RNA-binding proteins (RBP)-associated, intron pairing, and lariat-driven pathways— which can generate three types of circRNAs—exonic, intronic, and exon-intron circRNAs [65].

CircRNAs are key regulators of various biological processes of the body due to their unique structure. (1) CircRNAs acts as miRNA sponges to directly modulate miRNA functions, which in turn affects mRNA translation, this being the most common function of circRNAs. Indeed, this function was first proposed by *Hansen et al.*, who found that ciRs-7 circRNA in mouse brain can competitively suppress miR-7 activity, thereby modulating the expression of miR-7 target mRNAs [66]. (2) Other functions of circRNAs have been successively elucidated in recent years, such as interacting with RBPs to affect the translation of downstream mRNAs, directly binding ribosome for encoding functional peptides [67].

Therefore, circRNAs may play an important pathophysiological role in some psychiatric disorders (*e.g.,* depression [68-73], schizophrenia [74-77]) via certain underlying functions, including neurogenesis, neuro-inflammation, and autophagy [65]. Additionally, circRNAs may be used as valuable biomarkers for diagnosis and therapy due to their high stability and resistance to RNase R digestion, high evolutionary conservation, abundance in various eukaryotic cells, and cell-/tissue-specificity [78-80].

3.2. CircRNAs as diagnostic biomarkers for depression

Being an emerging field, limited number of studies provide valuable information on the role of circRNAs in regulating the pathological changes of depression. In 2016, *Cui et al.* published the first study to identify circRNA biomarkers of depression [68]. In PBMCs, four circRNAs significantly changed between five depressed patients and five healthy subjects, verified in an independent cohort (100 depressed patients and 103 healthy subjects) with consistent findings [68]. Additionally, in whole-blood samples, researchers found significantly reduced circFKBP8 and significantly increased circMBNL1 expression in depressed patients, which was verified in two independent cohorts [73]. The expression of these circRNAs also significantly correlated with the assessment scores of depressive symptomatology as well as with the levels of serum brain-derived neurotrophic factor protein and a neuroimaging-related indicator [73].

Further studies using cell culture and animal models have been also conducted to explore the underlying mechanisms of circRNA biomarkers in depression. In 2018, *Zhang et al.* found that plasma circDYM expression was significantly decreased both in depressed patients and in two depressive-like mouse models when compared with healthy subjects and normal mice, respectively [69]. Consistently, in vivo and in vitro research further demonstrated that circDYM expression can alter microglial activation by affecting miR-9 activity (targeting HECTD1 gene) [69]. In addition, in an independent cohort, including 60 depressed patients and 32 healthy subjects, significantly reduced expression of plasma circDYM was found in depressed patients [72]. Furthermore, a recent study revealed that the expression of circSTAG1 was significantly lower both in peripheral blood of depressed patients and in hippocampus tissues and peripheral blood of CUMS mouse [70]. This circRNA regulated m^6A methylation of fatty acid amide hydrolase mRNA to induce astrocyte dysfunction and subsequent depressive-like behaviours [70].

3.3. CircRNAs as therapeutic biomarkers for depression

Importantly, the circRNAs also showed therapeutic value in depression. In the ventral medial prefrontal cortex and hippocampus

Table 2
The association of microRNAs expression with effect of antidepressant therapy by human peripheral blood studies.

Study	Sample type	MiRNAs expression changes (after treatment *vs.* before treatment)		Treatment type	Length of treatment
		Significant upregulation	Significant downregulation		
Bocchio-Chiavetto et al. [59]	Whole-blood	miR-130b, miR-505, miR-29b-2, miR-26b, miR-22, miR-26a, miR-664, miR-494, let-7d, let-7g, let-7f, miR-629, miR-106b, miR-103, miR-191, miR-128, miR-502-3p, miR-374b, miR-132, miR-30d, miR-500, miR-589, miR-183, miR-574-3p, miR-140-3p, miR-335, miR-361-5p	miR-34c-5p, miR-770-5p	Escitalopram	12 weeks
He et al. [100]	Peripheral blood mononuclear cells	-	miR-124	Antidepressant treatment (not report)	8 week
Lin et al. [62]	Serum	miR-16 (only in selective serotonin reuptake inhibitors), miR-183, miR-212	-	Selective serotonin reuptake inhibitors or selective serotonin norepinephrine reuptake inhibitors	4 weeks
Feng et al. [55]	Plasma	miR-124	-	citalopram	8 weeks
Enatescu et al. [120]	Plasma	miR-1193, miR-4263, miR-3173-3p, miR-382, miR-3154, miR-129-5p, miR-3661, miR-1287, miR-532-3p, miR-608, miR-3691-5p, miR-2278, miR-3150a-3p, miR-375, miR-3909, miR-433, miR-937, miR-676, miR-1298, miR-489, miR-1909, miR-637, miR-1471	miR-744, miR-301b, miR-27a, miR-24, miR-146a, miR-126, miR-151-5p, miR-99b, miR-151-3p, let-7d, miR-221, miR-223, miR-181b, miR-146b-5p, miR-125a-5p, miR-26a, miR-652	Antidepressant treatment (not report)	12 week
Yrondi et al. [121]	Whole-blood	miR-103a-3p, miR-103b, miR-106a-5p, miR-106b-3p, miR-140-3p, miR-145-5p, miR-148b-3p, miR-151a-5p, miR-15a.5p, miR-15b-5p, miR-17-5p, miR-182-5p, miR-185-3p, miR-185-5p, miR-186-5p, miR-191-3p, miR-20a-5p, miR-20b-5p, miR-210-3p, miR-25-3p, miR-30a-5p, miR-30b-5p, miR-3158-3p, miR-3158-5p, miR-324-5p, miR-331-5p, miR-500a-3p, miR-502-3p, miR-532-5p, miR-550a-3p, miR-584-5p, miR-589-5p, miR-660-5p, miR-93-5p	miR-1301-3p, miR-200b-3p, miR-222-3p, miR-30c-1-3p, miR-3168, miR-328-3p, miR-505-5p, miR-744-5p, miR-92a-1-5p	Escitalopram	2 weeks
Lopez et al. [60]	Whole-blood	miR-1202	-	Desvenlafaxine	8 weeks
Fiori et al. [61]	Whole-blood	miR-135a and miR-16 (in one cohort), miR-1202 (in two cohorts)	-	Escitalopram or desvenlafaxine	8 weeks
Issler et al. [41]	Whole-blood	miR-135a	-	Cognitive behavioral therapy	12 weeks
Kuang et al. [103]	Serum	miR-451a	miR-34a-5p, miR-221-3p	Paroxetine	8 weeks
Lopez et al. [43]	Whole-blood	-	miR-146a-5p, miR-146b-5p, miR-425-3p, miR-24-3p	Duloxetine or escitalopram or nortriptyline or	8 weeks
Gururajan et al. [122]	Whole-blood	-	let-7b	Electroconvulsive therapy	Not report
Wang et al. [123]	Serum	-	miR-155	Citalopram	4 weeks
Li et al. [54]	Whole-blood	miR-335	-	Citalopram	4 weeks
Lopez et al. [44]	Whole-blood	miR-1202	-	Citalopram	8 weeks
Kolshus et al. [124]	Whole-blood	-	miR-126-3p, miR-106a-5p	Electroconvulsive therapy	Not report
Belzeaux et al. [29]	Peripheral blood mononuclear cells	miR-20b-3p, miR-433, miR-409-3p, miR-410, miR-485-3p, miR-133a, miR-145	miR-331-5p	Duloxetine, aripiprazole, mirtazapine, olanzapine, paroxetine, venlafaxine, escitalopram, fluoxetine, or lithium	8 weeks
Hung et al. [113]	Peripheral blood mononuclear cells	let-7e, miR-223, miR-146a, miR-155	-	Escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, bupropion, mirtazapine, or agomelatine	4 weeks

tissues of CUMS mice, *Zhang et al.* found that mmu_circ_0001223 expression was significantly increased after administration of total saponins from the leaves of Panax notoginseng, which showed an antidepressant role [81]. In addition, strong evidence indicated that restoring circDYM or circSTAG1 expression can significantly attenuate depressive-like behaviours in mice and improve microglial cell or astrocyte dysfunction, respectively [69,70], thus suggesting that these circRNAs may be potential therapeutic targets for depression.

To determine whether circRNAs can direct the clinical treatment of depression, direct evidence was provided firstly by *Cui et al.*, who detected that the PBMCs levels of hsa_circRNA_103636 significantly increased in depressed patients after treatment with antidepressants [68]. Furthermore, using physiotherapy or nerve regulation [*i.e.,* repetitive transcranial magnetic stimulation (rTMS)], *Song et al.* found a significant increase in plasma circDYM levels in depressed patients at the end of treatment and that circDYM can predict the response to rTMS treatment [72]. Recently, *Shi et al.* demonstrated that altered blood circFKBP8 levels can be recovered in depressed patients following effective rTMS treatment and that these were associated with the efficacy of antidepressant treatment [73].

3.4. Brief summary

CircDYM acts as miR-9 sponges to mediate the neuro-inflammation of CNS in depression and reduced plasma circDYM may be the most promising diagnostic biomarker of depression due to the ample supporting evidence. Meanwhile, after antidepressant treatment, plasma circDYM can predict the therapy response and be the potential indicator for the clinical treatment of depression. Furthermore, peripheral hsa_circRNA_103636, circFKBP8, circMBNL1, and circSTAG1 also display abnormal changes in depression and among them, circFKBP8 expression can be recovered after treatment, however, independent verification and/or comprehensive functional exploration is essential to further assess the clinical value of these circRNAs.

4. LncRNA

4.1. LncRNA biogenesis and function

LncRNAs are richly expressed transcripts with a length of over 200 nucleotides, which were initially reported in the developing mouse embryo by *Bartolomei et al.* [82] LncRNAs can be transcribed by RNA polymerase II from genomic loci, which is similar to mRNAs' generation and, in terms of molecular structure, most lncRNAs lack translated open reading frames, except for specific lncRNAs that contain cryptic open reading frames [83,84]. Based on their genomic location and structure, lncRNAs can be divided into five categories (intergenic, anti-sense, sense, intronic, and bi-directional), among which intergenic and anti-sense lncRNAs are the most common in humans [85].

LncRNAs can bind to DNA, RNA, and protein to exert many functions [86,87]. In the nucleus, lncRNAs can restrain and/or activate downstream gene expression by mediating chromatin modification and recruiting transcription factors. Additionally, lncRNAs can act as molecular decoys to remove proteins from a specific DNA location or as enhancers of gene activation. In the cytoplasm, lncRNAs can regulate multiple post-transcriptional processes, such as mRNA stability, miRNA sponge, and translation. Moreover, lncRNAs can also serve as scaffolds to combine different proteins for a higher-order complex.

Large and diverse amounts of lncRNAs have been found in the brain, which are involved in the regulation of important biological processes of the CNS [88]. Besides, lncRNAs also show abnormal expression levels in various tissues and cells in psychiatric diseases and have potential as diagnostic and therapeutic biomarkers due to their tissue-specific expression patterns, widespread expression, and high-efficiency of detection [89,90].

4.2. LncRNAs as diagnostic biomarkers for depression

It is essential to investigate the diagnostic value of lncRNAs in depression. In 2014, *Liu et al.* [91] investigated the genome-wide lncRNA expression in peripheral blood from depressed patients and reported four lncRNAs were upregulated in depression. They also described potential co-expression networks of differentially expressed lncRNAs and mRNAs, which provided direct evidence to support that lncRNAs can regulate the molecular pathogenesis of depression for the first time [91]. In addition, a well-designed study by *Cui et al.* revealed that six significantly downregulated lncRNAs (TCONS_00019174, ENST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707) were found in PBMCs from depressed patients compared with healthy subjects [92,93]. These results were further corroborated in an independent cohort, where significant correlations between the expression of these lncRNA expression and suicide risk were found in depressed patients [92,93]. Furthermore, *Ye et al.* observed a significantly increased LINC01108 expression and significantly decreased LINC00998 expression in peripheral blood leukocytes of depressed patients, compared with those of healthy subjects [94].

Additionally, several lncRNAs were also found in post-mortem brain tissue. In the anterior cingulate cortex tissue, nine lncRNAs showed a significantly differential expression between depressed and healthy subjects [95]. Among them, RP1-269M15.3 expression proved to be affected by a depression-associated single nucleotide polymorphism and was associated with depressive phenotypes [96]. Meanwhile, *Issler et al.* found a sex-specific lncRNA, LINC00473, whose expression was significantly reduced in the prefrontal cortex of depressed females but not of males, when compared with healthy subjects. This suggested that LINC00473 may be associated with female-specific stress resilience [97].

4.3. LncRNAs as therapeutic biomarkers for depression

To date, there is a paucity of knowledge regarding lncRNAs as therapeutic biomarkers, with related studies providing scarce information to assess the clinical value of lncRNAs for antidepressant treatment. In a previous study, after six weeks of formal antidepressant therapy, the levels of the above six lncRNAs in PBMCs of depressed patients were significantly higher than baseline levels and did not differ from those of healthy subjects [92]. Furthermore, *Liu et al.* reported that overexpression of NONHSAG045500 can inhibit transcription of serotonin transporter in SK-N-SH cells in vitro [98], and *Ni et al.* also found that the hippocampal expression level of TCONS_00019174 in CUMS mice can be recovered after imipramine treatment and that TCONS_00019174 may activate Wnt/β-catenin pathway to exert antidepressant-like effects [99].

4.4. Brief summary

Results on the above six peripheral lncRNAs are relatively consistent across different cohorts and demonstrate their influence on depressive symptoms (*e.g.,* suicide) and great potential for the clinical diagnosis of depression. Additionally, these lncRNAs can return to normal levels after antidepressant treatment and exhibit potential to be therapeutic biomarkers for depression. However, these findings need to be treated with caution due to lacking further independent verifications in other research groups, especially brain tissue-related findings, and in-depth function exploration in animal and cell models.

5. Conclusion

Multiple ncRNAs display aberrant expression in brain tissues and/or peripheral fluids of depressed patients, which may involve in the

core pathogenesis of depression and show prominent potential for the diagnosis of depression. (1) The 13 peripheral miRNAs with strong evidence have the consistent expression between CNS and peripheral circulation. (2) The peripheral circDYM exhibits consistent changes in depressed patients in independent studies and the same expression between depressed patients and depressive-like mouse models. (3) However, there is insufficient evidence to evaluate the most promising lncRNA biomarkers since they lack independent verification in other studies. (4) Furthermore, as important switches of gene expression, some peripheral ncRNAs expression changes are reported after antidepressant treatment and can serve as potential biomarkers to guide antidepressant therapy. In particular, compared with other ncRNAs, peripheral miR-1202, miR-16, and circDYM, exhibited relevantly definite regulatory mechanisms in depression, and their expression is associated with the clinical outcome of treatment and may predict the response to antidepressant therapy.

Although abnormal brain tissue and cerebrospinal fluid-derived ncRNAs may directly reflect pathological changes of CNS related to depression, unavailable samples make the examination more difficult than in peripheral blood samples (*e.g.,* plasma, serum). Furthermore, to date, despite the reviewed peripheral blood-derived ncRNAs have displayed consistent central and peripheral changes, no one published study measures ncRNAs levels in marked by specific nerve cell subtype in exosome of peripheral blood. After verifying originated in CNS, the ncRNAs of peripheral blood will be more convenient and valuable biomarkers for translation of clinical application in depression.

Despite the growing evidence about miRNA, circRNA, and lncRNAs in depression, many controversies and limitations still exist. Firstly, poor homogeneity and a small sample size in some studies may provide disputable findings, which affect the comprehensive assessments of ncRNA biomarkers in depression and does not favor clinical translation. Secondly, evaluation of the specificity of ncRNA biomarkers between depression and other psychiatric disorders, such as schizophrenia and bipolar disorder, is lacking in most studies, whereas it is indispensable for the precise diagnose and treatment of depression. Most importantly, although miRNAs, circRNAs and lncRNAs are abundantly expressed in the brain and peripheral circulation and play a pivotal role in regulating the pathogenesis of depression, whether their expression in the CNS correlates with in the peripheral circulation and whether peripheral ncRNAs are derived from CNS in the context of depression remain to be determined, which is a crucial factor for the development of convenient biological kits for the clinical practice. One more limitation but not last is that, since certain studies only demonstrated the impact of ncRNAs on depression in animal or cell models, translating these basic research findings into clinical application poses a considerable challenge.

The gene-environment interaction determined by epigenetic mechanisms, may be the main cause to induce the depression, and ncRNAs, as the important member of epigenetics, play crucial physiological and pathological roles in depression, such as regulation of monoamine neurotransmitter transmission, inflammation response, or neural plasticity. Additionally, ncRNAs can penetrate the blood-brain barrier based on their small molecule properties or the microvesicles transport, which make the detection of ncRNAs a potential non-invasive means to obtain CNS information from the peripheral blood. According to the principle of the multilevel verification (human/animal model; CNS/peripheral circulation), the present review found consistently aberrant expression of several ncRNAs between CNS and peripheral blood or in different cohorts, suggesting these ncRNAs may affect the target genes to result in depressive symptoms, including depressive emotion and suicidality, and be useful as diagnostic biomarkers for depression. Furthermore, the abnormal expression of ncRNAs can be reverted after antidepressant treatment and their changes are associated with the therapy response, which suggests that these ncRNAs may also serve as potential targets of therapeutic interventions and/or as therapeutic biomarkers for depression. Subsequently, these ncRNAs should be prioritized to determine the definite function in depression through more comprehensive researches, including depressive-like multi-species (*e.g.,* mouse, rat, and monkey) models, human-derived induced pluripotent stem cell /brain organoids, for promoting their clinical application. Meanwhile, by implementing interdisciplinary cooperation, especially the application of computer science, individualized diagnosis and treatment of depression based on the utilization of these ncRNAs as important members of a depression biomarker panel may become a reality.

Outstanding questions

To further investigate the potential values of ncRNAs and apply them into clinical translation for depression, *e.g.,* research and development of biological diagnostic kits and targeted candidate ncRNAs small interfering ribonudeoacid drugs, there is much to be optimized, including:

1. Multiomic data included microcosmic and mesoscopic data (*i.e.,* various genes / mRNAs / methylation / proteins / metabolites / neuroimaging features) and macroscopical information (*i.e.,* neuropsychological assessments), can provide more abundant evidence to reveal the underlying mechanism of ncRNAs in depression and are important for the all-sided evaluation of clinical value of ncRNAs as biomarkers.
2. More precise mechanism of ncRNAs in depression need to be investigated in the future study, particularly the identification of specific brain areas, neural circuits, and neuronal subtypes of ncRNAs' action.
3. As a highly heterogeneous psychiatric disorder, depression can be divided into different subtypes based on differential clinical characteristics (*e.g.,* attempted suicide, suicidal ideation, and non-suicidal thoughts) or neuroimaging features (*e.g.,* significantly increased or decreased amplitude of low-frequency fluctuations levels in some specific brain regions). The performance of ncRNA biomarkers for the diagnosis and treatment among these depression subtypes should be investigated.
4. As the important transporters of ncRNAs, circulating exosomes, especially CNS-derived exosomes (*e.g.,* neuron, astrocyte or microglial cell-derived exosomes), may be valuable objects to investigate the association of ncRNAs with depression.
5. Based on the findings of ncRNAs therapeutic biomarkers, RNA interference drugs discovery is a promising direction for achieving the precise or individualized medicine in depression. Meanwhile, new technologies, *e.g.,* adeno-associated viral (AAV) vector-mediated gene delivery, nano-drug delivery, will contribute to solving the predicament of blood brain barrier and achieve the antidepressive effectiveness by targeting ncRNA intervention in CNS.

Search strategy and selection criteria

Data for this review were identified by searches of PubMed, MEDLINE, and references from relevant articles using the search terms "non-coding RNA", "miRNA", "microRNA", "circRNA", "circular RNA", "lncRNA", "long non-coding RNAs", "major depressive disorder", and "depression". Only articles published in English were included up to April 2021.

Contributors

Zhijun Zhang contributed to the conception and design of the review. The first draft of the manuscript was written by Yachen Shi,

Qingyun Wang, and Ruize Song; Yan Kong and Zhijun Zhang critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no conflicts of interests.

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