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Research progress of miRNA in different depression model samples

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Abstract. Depression is a mood disorder characterized by prolonged depressed mood, lack of interest and pleasure, and low self-assessment. The miRNAs, as single-stranded non-coding RNA molecules that can participate in post-transcriptional regulation of gene expression, regulate physiological processes by degrading mRNAs or inhibiting the translation of their target genes to achieve gene silencing. Numerous studies have revealed an in-depth understanding of depression-related miRNA changes and the role they play in the pathogenesis of depression, and miRNAs have received widespread attention as therapeutic targets. This review summarizes the expression of miRNAs in different depression samples (patients, rats, and mice) and the corresponding regulatory pathways. The analysis revealed the existence of miRNAs with consistent expression trends in different samples, and the discovery of these miRNAs provides new insights into their use as therapeutic targets in depression.

Keywords: depression, miRNA, depression samples, regulation, therapeutic targets

1. Introduction

Major depressive disorder (MDD) is a mental disorder caused by a variety of factors, which seriously endanger the physical and mental health of human beings. Due to the high prevalence and recurrence of depression, it causes a serious socio-economic burden. According to a WHO report, MDD will be the first in the total global disease burden by 2030[1]. The most recent data indicate that the lifetime prevalence of MDD is 8%-12%[2]. The representative clinical symptoms of depression are persistent emotional depression, psychomotor depression, slow and dull thinking, and in severe cases, suicidal tendencies. Since the pathological mechanism of depression is not clear, depression relies more on pharmacological treatment except for treatment through psychological guidance. The most representative one is the monoamine neurotransmitter hypothesis, which suggests that the activity of monoamine transmitters in the brain is abnormal. Based on this hypothesis, the traditional antidepressant MAOI is used to increase the level of monoamine transmitters in the nervous system by inhibiting monoamine oxidase (MAO) to achieve antidepressant effects, but it has serious toxic side effects and is therefore no longer suitable for clinical application. New antidepressants such as Selective Serotonin Reuptake Inhibitor (SSRIs) can specifically block the reuptake of serotonin by the serotonin transporter (SERT) in presynaptic, thus increasing the interstitial serotonin concentration to achieve antidepressant effects. The biosafety is significantly better than that of conventional antidepressants, and even accidental overdoses do not have detrimental effects, increasing the likelihood that depressed individuals with suicidal thoughts would survive while on medication[3]. Some studies have shown that certain miRNAs (e.g., miR-16) aid in enhancing the antidepressant effects of SSRIs[4], suggesting that miRNAs may have therapeutic potential for depression.

MiRNAs are small endogenous non-coding single-stranded RNAs about 20-22 nucleotides long found in eukaryotes, highly conserved among species, expressed in a chronological and tissue-specific manner, and involved in the regulation of genes related to growth and development[5, 6]. MiRNAs are specifically expressed in human brain tissues and have significant regulatory functions in the brain, such as regulating synaptic plasticity or nervous system development[7-10]. Dysregulated miRNA networks are associated with human neurological disorders[11, 12]. Lopez et al. showed that miR-1202, a primate-specific miRNA, is enriched in the human brain and is differentially expressed in depressed patients[13], suggesting that miRNAs are associated with

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depression. The expression of miRNAs and how they are regulated in depression samples have been the subject of numerous studies in recent years, and some miRNAs (e.g. miR-200a-3p[14, 15], miR-199a-5p[16], miR-139-5p[17], etc.) are important regulators of the signaling pathway of depression. It has been demonstrated that inhibition of miR-146a-5p can alleviate depression-like behaviors[18], which may serve as one of the therapeutic targets for depression, revealing the potential contribution of miRNAs that may provide new therapeutic strategies for depression.

In this review, we concentrate on the research progress of miRNAs as a potential treatment element for major depressive disorder. After reviewing the existing literature, we investigate the changes in the levels of miRNAs acting as regulators and the related regulatory pathways from the perspective of different depression model samples and summarize the classification with the aim of finding reliable therapeutic targets for depression.

2. Regulatory mechanisms of miRNAs

The regulation of gene expression is a series of intricate reactions with spatial and temporal order in the process of genetic information from DNA to RNA to protein, containing multiple levels, such as operon models, mRNA maturation and degradation, transcription factor regulation, protein post-translational folding, and epigenetic regulatory mechanisms, etc. Phenotypic alterations may be brought on by variations in any one of these links[19-21].

With the deepening of understanding of epigenetics, researchers have gradually focused on the mechanisms of epigenetic regulation of gene expression. Non-coding RNA regulation is one of the epigenetic regulatory mechanisms, which has received widespread attention due to its important regulatory role in the growth and development of organisms, disease treatment, etc. Non-coding RNAs are RNAs that are not involved in protein codings, such as microRNAs (miRNAs), long-stranded non-coding RNAs (lncRNA), and Circle-RNAs (circRNAs), all of which can regulate gene expression and protein synthesis, but they function by different regulatory mechanisms[22]. LncRNAs play a cis-regulatory role at the chromosome-wide level[23], whereas the circRNAs act as competitive endogenous RNA sponges that adsorb miRNAs, thereby affecting the regulation of target mRNAs by miRNA[24]. In this paper, we focus on miRNAs that negatively regulate target gene (mRNA) expression at the genome level[25]. It has been shown that nearly 90% of human genes are regulated by miRNAs, and when the level of a miRNA is changed, the function of the gene it regulates is diminished or enhanced accordingly[26].

As a large family of gene regulators, miRNAs play a key role in the development of organisms, and their regulation of gene expression involves numerous protein-protein/protein-RNA interaction mechanisms[27]. In animal and plant cells miRNAs are usually widely expressed in the form of miRNA-induced silencing complexes (miRISCs)[28]. Most miRNAs, after forming a complex with RISC, complementarily pair with the target mRNA through the "seed region" (<10bp) at the 5' end, where the binding site is the 3' end of the untranslated region (UTR) of the target miRNA's end. The degree of pairing between the miRNA and the target mRNA determines the extent to which the miRNA/RISC complex inhibits mRNA expression, or the mechanism of induced gene silencing. If miRNAs can fully bind to target mRNAs, they can directly cleave or degrade mRNAs and block target gene expression, but usually, their binding is incomplete, thus affecting the effect of gene silencing. The incomplete binding of miRNAs to target mRNAs may inhibit gene expression to varying degrees through postinitiation mechanisms, co-translational degradation mechanisms, competitive inhibition mechanisms, ribosome formation inhibition mechanisms, and deadenylation mechanisms[28-30].

The miRNAs are abundant regulatory RNAs, and in addition to the regulatory approach of a single miRNA, miRNA-miRNA interactions can also affect the regulation of many key biological processes and influence gene expression[31, 32]. However, whether a single miRNA or several miRNAs are involved in the process, the outcome is still the silencing of target genes by inducing mRNA degradation, translation inhibition, or inducing the formation of heterochromatin to inhibit

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gene transcription, thereby regulating the physiological functions of the organism[33]. Since dysregulation of the miRNAs was discovered in the brains of depressed people, we can assume that one of the depression pathways that miRNAs regulate is also dysregulated, reflecting the pathological process of depression. MiRNAs thus play a crucial regulatory function in depression.

Postinitiation mechanisms: miRNAs promote premature dissociation of ribosomes to inhibit translation of target mRNAs.
Co-translational degradation mechanism: miRNAs do not inhibit the translational activity of polyribosome-coupled mRNAs, but cause premature termination and degradation of nascent polypeptide chains.
Competitive inhibition mechanism: the Argonaute protein of miRISC competes with eukaryotic initiation factor 4E (eIF4E) to bind to the cap structure of mRNA, inhibiting the formation of the translation initiation complex and thereby inhibiting translation.
Ribosome formation inhibition mechanism: Ago/RISC recruits eukaryotic initiation factor6 (eIF6), which inhibits translation initiation by preventing the binding of ribosomal large subunits and small subunits.
Deadenylation mechanism: Ago/RISC triggers the deadenylation of mRNA polyadenylate tails, preventing the formation of loop mRNA or decapping of the mRNA.

3. The miRNAs associated with depression

The miRNAs have important roles in the development and maturation of the nervous system, participating in a variety of pathophysiological processes in the brain and regulating the onset and progression of central nervous system diseases[34, 35]. Studies have shown that the onset of depression is influenced by epigenetics, and miRNAs, as an important factor involved in the regulation of gene expression, are closely associated with the onset and development of depression[36, 37].

A large number of previous studies are based on model organisms and samples from depressed patients, using methods such as gene microarray screening, combined with techniques such as biometric analysis[38] to investigate the correlation between miRNAs and depression. At present, most experimental depression samples are mainly divided into two categories: human and experimental animals, and due to a large number of miRNA family members and the wide range of regulatory pathways involved[8], the study of miRNAs in different samples is distributed in a punctiform manner, and the regulation of depression is a dynamic and balanced process, so the study of miRNAs focusing only on a certain miRNA cannot well elucidate the regulatory mechanism of depression. There is no systematic summary of the regulatory mechanisms and interrelationships of miRNAs in different depression samples. Therefore, by summarizing miRNAs in various depression samples, this study analyses miRNA that may be exploited as possible biomarkers or therapeutic targets and offers fresh perspectives for the treatment of depression.

3.1 Animal models of depression

To better treat depression, further research on its pathological mechanisms is needed to screen antidepressant drugs or treatments. Due to ethical constraints and the difficulty of obtaining patient samples, the vast majority of current research on miRNAs in depression has been conducted in animal models of depression. This research focuses on depression models in rats and mice due to their quick reproduction, brief gestation period, and significant gene similarity to human sequences[39].

3.1.1 Rat model

The research of depression-related miRNAs in rat depression models has centered on the brain. The prefrontal cortex (PFC) is known to be involved in mood regulation and other self-regulation[40, 41]. It has been suggested that dysregulation of miRNAs in the prefrontal cortex

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in depression may be closely associated with depressive conditions[14, 15, 42]. Wei et al. observed that eight miRNAs (miR-10a, miR-101b, miR-107, miR-124, miR-125a, miR-125b, miR-133a, miR-181a, miR-199a) were downregulated in the PFC of rats with hereditary MDD (Flinders sensitive lineage [FSL]), with miR-101b shown to target the SLC1A1 (glutamate transporter gene solute carrier family 1,member) to induce glutamate dysfunction and cause depression[42]. Chronic stress is one of the key triggers of MDD, and rats under a certain duration and intensity of stress may develop depressive behavior. miRNA expression levels differed under different durations of stress, and Satyanarayanan et al. found that in unpredictable chronic mild stress (UCMS) rats during stressful short-term stressors, PFC miR-200a-3p was downregulated in contrast to miR-200a-3p expression under chronic stress. Meanwhile, Yuan et al. demonstrated that the miR-200a/b-3p target PFC gene NR3C1, and that this gene's down-regulation led to an increase in the cleavage proteins caspase-3 and Bax and a decrease in the anti-apoptotic protein Bcl-2, accompanied by depression-like behaviors such as reduced neurogenesis, inflammatory activation, circadian rhythm disturbance, suggesting that miR-200a-3p may be a specific biomarker for central sensitization to depression[14,15]. Furthermore, Yuan et al. found that paeoniflorin could inhibit miR-200a/b-3p-mediated apoptosis and abnormal expression of apoptosis-related proteins in PFC neurons[15], which is enlightening for drug screening in depression.

Several researches have been carried out to target miRNA dysregulation in the hippocampus region since it has been proven that protein levels and metabolic changes in hippocampal tissue are strongly associated with the onset and development of depression[43]. As the hippocampus structures can be distinguished clearly, different studies will focus on depression-related miRNAs with different subdivisions. In the entire hippocampus, miR-144, which targets PTP1B (Protein Tyrosine Phosphatase 1B), showed significantly reduced expression, whereas miR-383 which targets Wnt2 (wingless-type MMTV integration site family member 2), had increased expression in chronic unpredictable mild stress (CUMS) rats. And altering the related miRNA levels both lead to elevated BDNF (brain-derived neurotrophic factor) expression, thus inhibiting apoptosis and inflammatory responses in hippocampal neurons and improving chronic stress-induced depression in rats[44, 45]. In the meantime, Huang et al. discovered that miR-17-5p bound to target mRNAs to a lesser extent than Nrf2 (nuclear factor erythroid-2-related factor 2) in the hippocampus of CUMS rats, and overexpression of Nrf2 competitively inhibited miR-17-5p expression, thereby promoting transcription of miR-17-5p-targeted Wfs1 (Wolfram Syndrome Protein 1) and alleviating cognitive dysfunction and brain inflammation mechanisms to achieve antidepressant effects[46]. In the hippocampal dentate gyrus (DG) of the depressed rat model, the expression of miR-26a-3p, miR-211-5p, and miR-204-5p was downregulated, involving activation of PTEN (phosphatase and tensin homolog)/PI3K (phosphatidylinositol 3-kinase)/Akt (protein kinase B) signaling pathway, Dyrk1A (dualspecificity tyrosine-(Y)-phosphorylation regulated kinase 1A)/STAT3 (signal transducer and activator of transcription 3) signaling pathway as well as aberrant expression of regulator of G-protein signaling 12 (RGS12), and overexpression of these miRNAs contribute to the inhibition of neuroinflammation, neuronal apoptosis, and depression-like behavior[47-49]. Thus, they are expected to be potential targets for the treatment of depression. In another study, Fan et al. unearthed that miR-146a-5p, carried in microglia-derived exosomes in rat hippocampal DG, inhibited the proliferation of neural stem cells and their differentiation into mature neurons by targeting the nuclear transcription factor KLF4, leading to a reduction in the number of newborn neurons, which in turn affected the integration and functional firing activity of hippocampal neural circuits and caused the development of depressive-like behaviors. Downregulation of miR-146a-5p alleviates neurogenesis deficits and depressive-like behaviors[18]. In light of these studies, it is anticipated that miR-26a-3p, miR-211-5p, miR-204-5p, and miR-146a-5p may operate as neuromodulation modulators in depression and represent prospective targets for treating the condition. Shen et al. found that miRNA-211-5p was significantly down-regulated in the CA1 hippocampus of a rat model of depression, and when it was up-regulated by inhibition of the Dyrk1A/ASK1 (Apoptosis signal-regulating kinase 1)/JNK (c-Jun N-terminal kinase) signaling

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pathway in the CA1 region ameliorated neuronal apoptosis and depression-like behavior in rats, and thus the miR-211-5p/Dyrk1A pathway may be heavily involved in the pathogenesis of depression[50]. As a result, hippocampus miRNA dysregulation-induced modifications in neuroplasticity, decreased neurogenesis, and neuronal apoptosis is essential factors in the development of depression, and all the miRNAs mentioned in this section may be useful as targets for treating depression.

It has been illustrated that miRNAs can regulate depression via controlling the glucocorticoid receptor (GR). In the PFC and hippocampus of rats, the levels of miR-218-5p, miR-124a, and miR-18a were negatively linked with GR levels, and all of these miRNAs were increased in depressed rats, resulting in vulnerability to depression[51, 52]. Studies have revealed that the hippocampus and hypothalamic-pituitary-adrenal (HPA) axis are responsive to GR signaling and play a major role in processing external stressors[53, 54]. In an antidepressant model constructed by overexpression of N-3 polyunsaturated fatty acids (PUFA) in rats, miR-218 and miR-182 levels were significantly reduced, while GR expression was increased, and the BDNF-5-hydroxytryptaminergic pathway was activated, affecting HPA axis function and thus producing antidepressant effects. The expression of miR-132 is still controversial, but it is also associated with GR-mediated downstream pathways in this antidepressant model. In contrast, the elevated expression of miRNA-155 after treatment with N-3 PUFA may be due to the downregulation of its target inflammatory transcription factor NF-κB (nuclear factor kappa-B), which reduces neuroinflammation and depression-like behavior[55-57]. In addition, it has been demonstrated in many studies that miR-218, miR-182, and miR-132 expressions are upregulated and miR-155 expression is downregulated in depression models[58-61].

According to studies, the amygdala is a critical component of the brain for producing, processing, and managing emotions, especially negative ones like fear. Depressed people frequently display uncontrollable low moods, which may be related to neuronal dysregulation of the amygdala[62]. Some studies have suggested that miRNAs may play an important role in this process[63-65]. Roy et al. identified 17 significantly up-regulated and 8 significantly down-regulated miRNAs in the amygdala of learned helplessness (LH) rats (Table 1), with the most significant increase in miR-128-3p expression[65]. The upregulation of miR-128-3p caused significant downregulation of key target genes of Wnt signaling (WNT5B, DVL1, and LEF1) and Arpp21 gene, which may be triggered by the amygdala-specific intracellular conversion mechanism of Arpp21, leading to depressive-like behavior[65]. In the basal lateral amygdala (BLA), depressive-like behavior in CUMS rats was favorably correlated with miR-124a levels and negatively correlated with miR-134 levels. miR-124a and miR-134 are involved in the regulation of FKBP5 (FK506 binding protein 5)/GR and CREB (cAMP-response element binding protein)-BDNF signaling respectively to induce depressive-like behavior generation[66, 67]. Additionally, Yu et al. encountered that ginsenoside Rg1 has the potential to be used in clinical trials for the treatment of depression because it may activate the CREB-BDNF system within the BLA by controlling miR-134 to reduce chronic stress-induced neuronal structural abnormalities and biochemical changes[67].

3.1.2 Mouse model

The sample region examined in a study on depression-related brain miRNA alterations in mice was comparable to that in rats. Ma et al. used high-throughput sequencing of mRNAs and miRNAs in the medial prefrontal cortex (mPFC) of CUMS mice and found that 17 miRNAs were upregulated[68] (Table1), while the levels of their associated mRNAs were downregulated, consistent with the previously described mechanisms of miRNA-mediated mRNA regulation, suggesting that depression-related genes and pathways are regulated by miRNAs. miRNA dysregulation-mediated inflammatory responses are widespread in depression, and Wang et al. identified three significantly differentially expressed miRNAs (miR-194-5p, miR-25-3p down-regulated, and miR-125a-5p up-regulated) and 119 associated mRNAs in the PFC of mice with chronic social defeat stress (CSDS) depression by analyzing the miRNA microarray dataset associated with MDD, and miRNAs differential expression was responsible for the aberrant

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inflammatory response as well as depression-like behavior characterized by disturbed Th17 cell differentiation important factors[69]. Studies have shown that the PFC is an important target of stress-induced damage to the organism[70]. In both the mouse failure stress model and the chronic social stress model, miR-218 - 5p and miR-98-5p were found to be downregulated in the PFC, and their overexpression alleviated depression-like behaviors in mice, with the former possibly acting as a post-transcriptional repressor that ameliorates stress disease susceptibility and vulnerability induced by its target Netrin-1 guidance cue receptor DCC; while the latter's upregulation can be induced with ketamine, thus both miRNAs may have therapeutic potential as targets in the treatment of depression[71, 72].

One of the key areas of the brain that maintains neurogenesis is the hippocampus[73], and BDNF is a key regulator of neuroplasticity. Abnormalities in either of these areas are intimately associated with the development of depression[74]. MiRNAs in the hippocampus have been reported to be crucial for the regulation of BDNF and to play a significant role in depression[16, 17, 75, 76]. In the hippocampus of depressed mice, miR-139-5p, miR-199a-5p, and miR-124 expression was upregulated, and miR-134 expression was downregulated by mechanisms involved in regulating the BDNF-TrkB (tyrosine kinase receptor B) signaling pathway, acting on WNT2 and CREB/BDNF signaling pathways, regulating BDNF biosynthesis, and binding directly to the 3'UTR of BDNF[16, 17, 75, 76] that induce depression-like behavior. Interestingly, Zhang et al. combined in vitro and animal experiments to verify that adenosine deaminase (ADAR1), which acts on RNA1, is involved in antidepressant effects through miR-432 regulation of BDNF[77]. However, whether this mechanism occurs specifically in the hippocampus has not been elucidated. It is speculated that there may be a group of miRNAs that regulate the activity of this pathway on neurons and synapses at different nodes of BDNF signaling, which in turn affects the development of depression, and thus this group of miRNAs has potential as a biomarker of depression. In a mouse model of post-stroke depression (PSD), it has been demonstrated that there are 21 highly up-regulated and 32 significantly down-regulated miRNAs[78]. Among them, miR-129-5p and miR-34b-3p both shows reduced expression in the hippocampus, with the former causing neuronal damage by targeting four genes of autophagy-related proteins (SCOC/ULK1/NBR1), thereby forming a protein-FEZ1 complex[79], and the latter provokes a neuroinflammatory response by targeting eukaryotic translation initiation factor 4E (eIF4E), activating microglia in the hippocampus and leading to depression[80]. The differentially expressed miRNAs and mRNAs screened in these studies provide a theoretical basis for further investigation of the relevant molecular mechanisms and offer creative solutions for the early diagnosis, prevention, and treatment of depression.

One of the hallmarks of serious depression is recurrent unpleasant mood, and the amygdala has been praised in depression studies for its role in emotion processing[62]. Both sequencing of mRNA and miRNA in the amygdala of depressed mice and validation of mRNA and miRNA profiles for stress susceptibility and resilience to induced psychological stress in the amygdala leads to the conclusion that miRNA dysregulation, as well as downregulation of genes related to synaptic function and imbalance of signaling pathways within the amygdala, are associated with major depression[81, 82]. In addition to this, in the bed nucleus of the stria terminalis (BNST), Luo et al. confirmed gender differences in miRNA susceptibility to stress-induced depression, finding that Let-7a, let-7f, and miR-181a-5p were upregulated in stressed female mice, but not in male mice[83].

3.2 Patient Tissue

Due to our current lack of consensus on the pathology and etiology of depression, there is a large gap between experimental animals and humans, which cannot fully simulate some of the core symptoms of depression, such as low mood, feelings of worthlessness, and recurrent thoughts of death or suicide[84]. The extent to which animal models of depression reflect human pathophysiological processes is also uncertain, and therefore the results of animal models are not

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directly applicable to humans. Hence, experiments based on patients with depression are more convincing, and some studies have been conducted on patients with depression.

3.2.1 Patient brain tissue

It has been noted that the volume of brain areas such as the cortical areas, hippocampus, and amygdala tends to decrease in most depressed adult brains, and reduced white matter integrity is frequently seen[85]. However, the underlying molecular mechanisms are still unknown. Many studies have now found that miRNAs are differentially expressed in the brain in depressed and healthy individuals, and some studies have reported that key genes of signaling pathways in MDD are regulated by miRNAs[86]. These pathways have important effects concerning neurogenesis and synaptic plasticity, revealing that miRNA may be involved in the disease progression process in MDD.

As the primary sample, the postmortem brains of MDD patients who committed suicide have been studied to determine the expression levels and regulation mechanisms of miRNAs. In the PFC of deceased depressed patients, Smalheiser et al. identified 21 miRNAs with significantly downregulated expression (Table1) and a set of miRNAs that showed high co-regulation only in depressed suicidal individuals[87]. Yoshino et al. showed that six miRNAs (miR-215-5p, miR-192-5p, miR-202-5p, miR-19b-3p, miR-423-5p, miR-219a-2-3p) were significantly upregulated and two miRNAs (miR-511-5p, miR-483-5p) were significantly downregulated in the dorsolateral prefrontal cortex (dlPFC) of MDD patients by miRNA sequencing analysis[88]. In postmortem mPFC samples, Gorinski et al. found that endogenous miRNAs miR-30a and miR-200a were upregulated and downregulated respectively[89]. The dysregulation of these miRNAs is significantly associated with the disruption of multiple signaling pathways, such as PI3K/Akt, ERK (extracellular regulated protein kinases)/MAPK (mitogen-activated protein kinase), Rac, IGF (insulin-like growth factor), and cell cycle disruption, and is closely linked to the pathogenesis of depression. 5-HT receptor overexpression is a possible mechanism in the pathogenesis of depression[90]. A study detected elevated miR-30e expression in the mPFC of DS (diet by suicide) patients with MDD and confirmed that miR-30e negatively regulates the palmitoyltransferase ZDHHC21, reduces palmitoylation of the 5-HT1AR, decreases the signaling function of the 5-HT1AR[89] and thus induced depression-like behavior. In a different study, Morgunova et al. explained the potential pathogenesis of adolescent depression by demonstrating that decreased levels of miR-218-5p and increased levels of Netrin-1 receptor DCC were significantly associated with altered synaptic plasticity in the dendritic spine region of PFC pyramidal neurons in adult patients with MDD who died by suicide[71]. This demonstrates that miRNAs target a variety of signaling pathways and can control the development and course of depression by modifying these signals.

In addition to the prefrontal cortex of depressed suicide patients, in other brain regions, miR-326 levels are reduced in the Edinger-Westphal nucleus (EWcp) of depressed suicide attempters or completers, along with elevated levels of urocortin 1 (Ucn1), and miR-326, an upstream regulator of Ucn1 neuropeptide expression in midbrain neurons, regulates the brain's response to stress by altering binding to Ucn1 mRNA 3′- UTR binding, modulates the brain's response to stress and depression[91]. In a separate article, Roy et al. observed that the expression of 13 miRNAs was substantially changed in the locus coeruleus (LC) of depressed suicidal individuals, with 10 of them being upregulated (miR-17-5p, miR-20b-5p, miR-106a-5p, miR-330-3p, miR-541- 3p, miR-582-5p, miR-890, miR-99b-3p, miR-550-5p, miR-1179) and three were down-regulated (miR-409-5p, let-7g-3p, miR-1197), and based on the hypothesis that these miRNAs and their target genes constitute particular regulatory networks that may be connected to the neurobiological mechanisms underlying suicide[92].

3.2.2 Patient body fluids and exosomes

The study faces challenges due to a scarcity of samples and restrictions on the ability to detect specific activity indicators when collecting brain samples from MDD patients. In contrast, patient

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body fluids are more readily available, and qRT-PCR allows accurate quantitative quantification of miRNA, making it easier to examine them. Moreover, several studies have shown that miRNA can not only exist in patients' brain tissue or cerebrospinal fluid (CSF), but also be encapsulated in exosomes and released into the blood by crossing the blood-brain barrier, and miRNA detected in the blood can reflect the alteration of miRNA in the brain[93]. We anticipate using miRNA variations in body fluids as a monitoring signal of depression because miRNA has the potential as a biomarker in neurological illnesses.

Cerebrospinal fluid is a colorless and transparent fluid present in the ventricles and subarachnoid space, and the changes in miRNA content in it may reflect the signal changes of related pathways in the brain, and these signal changes cause neuronal or synaptic changes, reflecting the changes of neurological diseases like depression, so we inferred that miRNA is also used as one of the detectors of depression[94]. Researchers examined the cerebrospinal fluid of MDD patients and figured that miR-139-5p and miR-199a-5p expression levels rose, with the latter being more strongly upregulated. Further evidence from animal studies indicated that miR-199a-5p targets WNT2 and modulates CREB/BDNF signaling, hence accelerating the pathological process of depression[16]. Another research concluded that the miR-16 gene was considerably downregulated in the CSF of MDD patients. This could have been accomplished by targeting the SERT gene to regulate the serotonin neurotransmitter system, which is implicated in the physiopathological process of MDD[95]. Consequently, it is anticipated that miRNAs found in the cerebrospinal fluid will be crucial in the management of depression.

Peripheral blood miRNAs' physicochemical characteristics are extremely stable, and their expression is tissue-, time-, and disease-specific. Blood collection is simple and affordable, enabling dynamic clinical surveillance of miRNA expression levels[96]. When Liu et al. did a miRNA expression array analysis on peripheral blood mononuclear cells (PBMCs) from MDD patients and healthy controls (HCs), they discovered that the MDD group had notably lower expression levels of miR-374b and miR-10a compared with HCs, while the levels of the 2 miRNAs showed a significant upward trend after treatment, suggesting that they may be involved in the biological mechanism and therapeutic response of MDD[97]. This offers novel suggestions for MDD therapeutic targets. Regarding peripheral blood miR-132, it was shown that[98, 99] depressed patients had significantly higher levels of miR-132 expression in peripheral blood leukocytes and plasma than did healthy controls, which is consistent with the expression trend in CUMS rat models. MiR-132 has also been demonstrated to be a known regulator of BDNF[100]. Therefore, through controlling stress-induced neural plasticity and neuronal survival in depression, miRNA-132 may have an impact on the onset and progression of depression. Moreover, Li et al. mentioned that miR-182 levels were negatively correlated with BDNF levels in patient serum[101], which was consistent with the trend of miR-132/BDNF[100], perhaps these two miRNAs regulate depression by jointly targeting BDNF, though the precise mechanism needs to be further explored.

The presence of miRNAs in exosomes can also be detected, and since they are contained in exosomes, their characteristics are stable and simple to gather and measure[102]. Exosomal miRNAs have been used in a range of studies on depression[103-105]. Jiang et al. found that miR-186-5p was upregulated in peripheral blood exosomes of MDD patients and that it had a targeting effect on SERPINF1 (Serpin Family F Member 1), further confirming that miR-186-5p suppression alleviated depression-like behavior in depressed mice[103]. Wei et al.[104] found that the most differentially expressed exosomal miRNA in depressed patients was miR-139-5p (up-regulated), which is thought to be a negative regulator of neural stem cell proliferation and neuronal differentiation, regulating neuronal physiological processes and thus influencing the pathological process of depression, so we inferred that miR-139-5p is a promising target for the treatment of MDD[104]. According to Xian et al., miR-9-5p can transfer exosomally from neurons to microglia, activating M1-type microglia and leading them to release pro-inflammatory cytokines that further damage neurons. The mechanism may be that miR-9-5p overexpression inhibits the SOCS2 (suppressor of cytokine signaling 2) and activates the JAK (Janus kinase)/STAT3 pathway,

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leading to neuronal injury, which is consistent with the validation results in CUMS mice, thus miR-9-5p expression is expected to be a new therapeutic for MDD target[105].

3.2.3 Patient skin

Dysregulated miRNAs in skin fibroblasts from depressed patients may serve as biomarkers and aid in clinical diagnosis. Creating two metabolic stresses, galactose (GAL) medium or reduced lipid (RL) medium, Garbett et al. found that abnormal molecular responses of miRNAs were observed only in fibroblasts with MDD, which were shown to induce upregulation of miR-296-5p expression, a regulator of I-kappa-B kinase, enhancing the pathological response to depression[106]. Based on Garbett, Kaadt et al. used the flash-frozen skin technique in a rat model to study 38 regulated miRNAs in fibroblasts from depressive individuals and identified miR-450a, miR-185, and miR-193a (upregulated) as the most promising biomarker candidates[107].

There are currently fewer studies on depression-related miRNAs in the skin, which is probably related to a combination of factors, including the challenge of maintaining fibroblasts' physiological activity in vitro and the lack of correlation between miRNAs in the skin and depression, leading to bottlenecks in this field of research and difficulties in project implementation. However, the flash-freezing skin technology used by Kaadt[107] has some cutting edge and is expected to play a role in the detection of depression-related indicators.

4. Discussion

Depression is an affective psychiatric condition with a complex etiology that is characterized by a sad mood, lack of enjoyment, and cognitive and sleep disturbances[108]. MiRNAs have a great deal of potential as therapeutic targets and potential biomarkers for depression, according to a slew of studies published in recent years that demonstrate their involvement in several classical pathogenesis of depression and their capacity to regulate the expression of important proteins by targeting genes in multiple nodes. To provide an overview of the state of miRNA research, this review emphasizes patient and animal samples.

Our study found that miR-17-5p, miR-330, miR-582-5p, miR-132, miR-182 (up-regulated) and miR-101, miR-200, miR-10a (down-regulated) were shown to have the same altered expression in depressed patients and rats, and miR-30e, miR-139-5, miR-199a-5p (up-regulated) and miR-155 (down-regulated) had the same expression trend in depressed patients and mice. Since the findings of these miRNAs are more trustworthy, these miRNAs are quite likely to be therapeutic targets for depression. Among them, we found different results regarding miR-132 expression in the hippocampus in the two studies. In the therapeutic model of depression, While Choi came to the conclusion that N-3 PUFA had no influence on the expression of miR-132 or that the effect was insignificant, Kim et al. discovered that N-3 PUFA downregulated miR-132[55-57]. Both studies utilized rat models in which chronic mild stress (CMS) and maternal separation (MS) together caused depression, but Choi used female rats in which both ovaries were removed, so the physiological status of the rat samples and the degree of depression in both studies could not be completely consistent. When combined with the cumulative impacts of environmental, genetic, temporal and spatial, and other factors, we hypothesize that this is one of the reasons for the inconsistent degree of miR-132 changes in the hippocampus observed between the two groups. However, it was determined that the expression of miR-132 was elevated in the blood of depressive patients[98]. Together, we propose that miR-132 inhibition plays a significant part in the remission of depression.

Interestingly, opposite alterations in miR-200a-3p levels were observed in rat PFC during short-term and long-term stress, according to a study[14]. MiR-200a-3p is known to be elevated in the mPFC of patients with major depression[89] speculating that the paradoxical decrease in miR-200a-3p in depressed rats during long-term stress may be related to neuroprotection, reflecting a self-regulatory role of the organism. MiR200a-3p has been underlined to precisely target genes in pathways linked to diseases like neuropathic pain, inflammation, metabolism, and neurogenesis[14].

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Therefore, further development of therapeutic approaches targeting miR-200a-3p is expected to personalize the treatment of individuals suffering from depression.

We found that miR-218 can alter depression susceptibility by targeting different genes. Due to its regulation of different pathways, we observed that its expression profile is different in depressed individuals, e.g. miR-218 is down-regulated when targeting DCC[71] and is upregulated when targeting certain CNS genes[52]. Ultimately, they all together lead to depression. However, this miRNA is not favorable as a therapeutic target because its expression profile is not consistent and specific enough in depressed patients, making it easy for its altered expression to cause dysregulation of other pathways.

Besides, miR-124, miR-125, miR-181, and miR-199 were found to be downregulated in a study on a genetic rat model of MDD (Flinders sensitive line [FSL]) [42], whereas their expression was considered to be elevated in other depression models, such as CUMS, CSDS animals, and patients' cerebrospinal fluid[16, 51, 69, 83]. The diverse depression techniques employed on the samples in various trials could be to blame for the discrepancy in results. FSL rats are a transgenic animal model whose depression method belongs to congenital depression, while most depressed patients nowadays are induced to develop depressive behaviors due to external stimuli later in life, so animal models like CUMS and CSDS also adopt the method of acquired depression, which can better simulate the real onset and development of depression. Real-life genetic depression is, after all, a minority, so we prefer to study miRNA changes in depressed samples caused by external stress. Furthermore, the true reason for the observed variations in miRNA alterations between congenital and acquired depression has not been uncovered.

In summary, this review explores the function of miRNAs in the pathogenesis of depression and their promise as therapeutic targets based on different depression samples. The study of miRNAs in the pathophysiology and therapy of depression is still in its infancy, and more work has to be done to elucidate many of the miRNAs and the regulatory mechanisms that underlie them. A new direction for the understanding of the pathophysiology of depression and its diagnosis and therapy can be found in the miRNAs that are identically expressed in many samples as identified in this review.

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Table 1. miRNA expression changes in different depression samples

Sample	miRNAs	References
Rat PFC	Upregulated: miR-124a, miR-18a[51]	[51]
	Down-regulated: miR-10a, miR-101b, miR-107, miR-124, miR-125a, miR-125b, miR-133a, miR-181a, miR-199a[42] , miR-200a/b-3p[14, 15]	[42],[14, 15]
Mouse PFC	Upregulated: miR-148b-5p, miR-879-5p, miR-144-3p, miR-540-5p, miR-582-5p, miR-15b-5p, miR-210-5p, miR-871-3p, miR-3103-5p, miR-16-1-3p, miR-470-5p, miR-190b-5p, miR-384-5p, miR-490-5p, novel_mir_46, novel_mir_214, novel_mir_213[68] , miR-125a-5p[69]	[68],[69]
	Down-regulation: miR-194-5p, miR-25-3p[69] , miR-218 - 5p[71] , miR-98-5p[72]	[69],[71] ,[72]
Human PFC	Down-regulated: miR-142-5p, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR-20b, miR-376a*, miR-190, miR-155, miR-660, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p[42] , miR-218-5p[71]	[42],[71]
Human dlPFC	Up-regulated: miR-215-5p, miR-192-5p, miR-202-5p, miR-19b-3p, miR-423-5p, miR-219a-2-3p[88]	[88]
	Down-regulated: miR-511-5p, miR-483-5p[88]	[88]
Human mPFC	Upregulation: miR-30e, miR-30a[89]	[89]
	Down-regulation: miR-200a[89]	[89]
Rat hippocampus	Up-regulation: miR-383[45] , miR-17-5p[46] , miR-218[52, 55-57] , miR-124a, miR-18a[51] , miR-132[55] , miR-182[55-57]	[45],[46] ,[52, 55-57] ,[51] ,[55] ,[55-57]
	Down-regulation: miR-144[44] , miR-155[55-57]	[44],[55-57]
Rat hippocampus DG	Upregulated: miR-146a-5p[18]	[18]
	Down-regulation: miR-26a-3p[47] , miR-211-5p[48] , miR-204-5p[49]	[47],[48] ,[49]
Rat hippocampus CA1	Down-regulated: miRNA-211-5p[50]	[50]
Mouse hippocampus	Upregulation: miR-139-5p[17] , miR-199a-5p[16] , miR-124[75] , miR-432[77]	[17],[16] ,[75] ,[77]
	Down-regulation: miR-134[76] , miR-129-5p, miR-34b-3p[78]	[76],[78]
Rat amygdala	Upregulated: let-7e-5p, miR-128-3p, miR-128-3p, miR-132-3p, miR-132-5p, miR-30c-2-3p, miR-330-5p, miR-342-3p, miR-361-3p, miR-425-5p, miR-431, miR-672- 5p, miR-674-3p, miR-674-5p, miR-873-3p, miR-novel-chr2_36612, miR-novel-chr7_57810[65]	[65]
	Down-regulated: miR-292-5p, miR-293-5p, miR-298-3p, miR-34c-5p, miR-7b, miR-novel-chr12_7501, miR-novel-chr17_19917, miR-novel-chr20_32221[65]	[65]
Rat BLA	Upregulation: miR-124a[66]	[66]
	Down-regulation: miR-134[67]	[67]
Mouse BNST	Upregulation: Let-7a, miR-30e, let-7f, miR-181a-5p[83]	[83]
Human EWCP	Down-regulation: miR-326[91]	[91]
Human LC	Up-regulated: miR-17-5p, miR-20b-5p, miR-106a-5p, miR-330-3p, miR-541-3p, miR-582-5p, miR-890, miR-99b-3p, miR-550-5p, miR-1179[92]	[92]
	Down-regulated: miR-409-5p, let-7g-3p, miR-1197[92]	[92]
Human CSF	Up-regulated: miR-139-5p, miR-199a-5p[16]	[16]
	Down-regulation: miR-16[95]	[95]
Human blood	Up-regulated: miRNA-132[98, 99] , miR-182[101]	[98, 99],[101]
	Down-regulation: miR-374b, miR-10a[97]	[97]
Human exosomes	Upregulation: miR-139-5p[104] , miR-186-5p[103] , miR-9-5p[105]	[104],[103],[105]
Human skin	Upregulated: miR-296-5p[106]	[106]

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fibroblasts		
Rat skin fibroblasts	Upregulated: miR-450a, miR-185, miR-193a[107]	[107]

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