

MicroRNA as therapeutic targets for treatment of depression

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Abstract: Depression is a potentially life-threatening mental disorder affecting approximately 300 million people worldwide. Despite much effort, the molecular underpinnings of clinical depression remain poorly defined, and current treatments carry limited therapeutic efficacy and potentially burdensome side effects. Recently, small noncoding RNA molecules known as microRNA (miRNA) have gained prominence as a target for therapeutic intervention, given their capacity to regulate neuronal physiology. Further, mounting evidence suggests a prominent role for miRNA in depressive molecular signaling. Recent studies have demonstrated that dysregulation of miRNA expression occurs in animal models of depression, and in the post-mortem tissue of clinically depressed patients. Investigations into depression-associated miRNA disruption reveals dramatic effects on downstream targets, many of which are thought to contribute to depressive symptoms. Furthermore, selective serotonin reuptake inhibitors, as well as other antidepressant drugs, have the capacity to reverse aberrant depressive miRNA expression and their downstream targets. Given the powerful effects that miRNA have on the central nervous system transcriptome, and the aforementioned studies, there is a compelling rationale to begin to assess the potential contribution of miRNA to depressive etiology. Here, we review the molecular biology of miRNA, our current understanding of miRNA in relation to clinical depression, and the utility of targeting miRNA for antidepressant treatment.

Keywords: depression, microRNA, miRNA, BDNF, Dicer, serotonin

Introduction

Clinical depression is a chronic mood disorder affecting nearly 300 million people worldwide, with a lifetime prevalence of approximately 19% of the population.¹⁻³ With potentially life-threatening consequences, depression is a major health concern characterized by low mood, anhedonia, disturbance of sleep and appetite, and feelings of despair, shame, and guilt. Dysregulation of monoamine signaling has long been considered central to depressive neuropathology, but the downstream molecular etiology of clinical depression is ill defined. Consequently, the ability to quickly and effectively alleviate the multitude of clinical symptoms remains elusive. There is a pressing need for therapeutics that will quickly and selectively target the pathophysiological underpinnings of clinical depression, without the many off-target side effects associated with current antidepressants. Within this context, we describe the role that micro ribonucleic acid (miRNA) dysregulation may play in depression, and the potential therapeutic value of targeting miRNA. miRNA are a subclass of ~22 nucleotide (nt) noncoding RNA species that function principally by disrupting target messenger RNA (mRNA) expression. miRNA have garnered interest as potential therapeutic targets for

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an array of disorders of the central nervous system (CNS).^{4–6} More specifically, miRNA show remarkable potential in the treatment in mood disorders, and specifically in the treatment of clinical depression.^{7,8}

The molecular pathophysiology of depression

Clinical depression is associated with a range of cellular and molecular deficits within the CNS. For decades, the monoamine hypothesis of depression dominated in its assertion that dysregulation of serotonergic, noradrenergic, and dopaminergic signaling was at the core of depressive etiology.⁹ Stemming from the clinical efficacy of first-generation monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) targeting these systems, the monoamine hypothesis asserts that each depression-associated symptom stems from deficits in respective neurotransmitter signaling. This hypothesis also spawned a subsequent generation of antidepressants targeting the serotonin transporter (SERT) that are known collectively as selective serotonin reuptake inhibitors (SSRIs). Along these lines, patients with deficits in the serotonin transporter gene (5-HTT) are significantly more likely to develop depressive symptoms following stressful life events.¹⁰ Similarly, antidepressants known as norepinephrine reuptake inhibitors (NRIs) have been used to target the norepinephrine transporter (NET). This strategy can also be used in conjunction with those targeting SERT (thus, serotonin-norepinephrine reuptake inhibitors, SNRIs) and those targeting the dopamine transporter (DAT).¹¹ Nevertheless, evidence supporting monoamine signaling as the direct precipitating factor in depressive pathogenesis is lacking.

Some progress has been made in our understanding of specific depressive pathophysiological mechanisms. The raphe nuclei, locus coeruleus, prefrontal cortex, amygdala, and hippocampus all show markedly reduced volumes and neuronal density in patients diagnosed with major depressive disorder.^{12–15} Dysregulation of structural plasticity, synaptic connectivity, and dendritic morphology are thought to contribute to depressive pathophysiology.^{16,17} Deficits in neurogenesis and neuroplasticity within the hippocampus have also been linked to dysthymia and depression-associated memory loss, and can be alleviated by increases in serotonin signaling following treatment with antidepressants.^{18–20} Excessive glutamatergic neurotransmission is also partially alleviated by antidepressants, and *N*-methyl-D-aspartate (NMDA) receptor antagonists are known to reduce depressive symptoms.^{21,22}

Brain-derived neurotrophic factor (BDNF) signaling is of particular interest in understanding the molecular

etiology of depression, and has led to the development of a neurotrophic hypothesis of depression.²³ BDNF within the amygdala and the anterior cingulate cortex is protective against the depression-associated polymorphisms of the serotonin transporter.²⁴ Concordantly, circulating levels of BDNF are markedly reduced in patients with depression, and increases in serotonin activity following SSRI treatment may contribute to a restoration of BDNF activity.^{25,26} Downstream second messenger signaling pathways involving mitogen-activated protein kinase/ERK (MEK)1, extracellular signal-regulated protein kinase (ERK)1/2, Raf-1, and B-Raf are altered in both animal models of depression and in the post-mortem brains of depressed suicide victims.^{27–32} In addition, phosphoinositide 3 (PI-3)-kinase, protein kinase A (PKA), and protein kinase C (PKC) signaling all show depression-associated down-regulation.^{33–36} Unsurprisingly, therefore, decreased activation of the downstream transcription factor cyclic adenosine monophosphate (cAMP) response element-binding (CREB) is a prominent feature in both post-mortem tissue and animal models of depression.^{37,38}

In addition to neuronal deficits, glial cell dysfunction and cell loss has also been associated with depression.^{39,40} Further, there is increasing evidence for a neuroimmune and microglial component to depressive pathophysiology.⁴¹ In line with this idea, depressive symptoms are closely associated with the behavioral effects associated with systemic infection, and expression of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α are increased in patients with depression.^{42–44} Excess glucocorticoid and cortisol activity contribute to an overactive hypothalamic–pituitary–adrenal (HPA) axis, which can both precipitate and perpetuate depressive episodes.^{45–47}

Disturbances in circadian clock timing are also closely associated with clinical depression.^{48,49} Serotonergic and glutamatergic innervation within the suprachiasmatic nucleus (SCN) yields it particularly vulnerable to the dysregulation of those neurotransmitters. Projections from the SCN to the hypothalamus also exacerbate imbalance within the HPA axis. Further, depressed patients experience a decreased latency to enter rapid eye movement (REM) sleep, which lasts longer and occurs with greater frequency than in non-depressed individuals.^{50,51} Given that REM sleep requires reduced serotonin levels within the brainstem, it may not be surprising that such symptoms are alleviated by SSRI antidepressants.^{52,53} Likewise, sleep deprivation has been shown to ameliorate depressive symptoms and to induce serotonin signaling.^{54,55}

Despite these advances in the understanding of the molecular underpinning of clinical depression, much is lacking with respect to pharmacological strategies for treatment. Hence, serotonergic and noradrenergic signaling still serve as the primary targets of modern antidepressants. These treatments yield relatively modest symptomatic relief across the population, and the therapeutic effects often do not manifest for weeks, or even months, after initiation.⁵⁶ In the absence of a more nuanced understanding of the molecular mediators in clinical depression, pharmacological progress will remain stymied. Given the array of biological processes affected by, and contributing to, clinical depression, it is unlikely that treatment targeting any single aspect of depressive pathophysiology will be broadly effective. Rather, therapeutics that modulate multiple branches of depressive etiology may prove advantageous. Such ‘master’ regulators could provide systemic homeostatic control for disorders of neuronal signaling. Thus, targeting multiple nodes of depressive pathophysiology has the potential to provide relief in patients whose symptoms are unresponsive to the current standard antidepressants. As the regulatory potential of noncoding RNA becomes more fully appreciated, miRNA have begun to garner attention as potential targets for the treatment of clinical depression.

MicroRNA biogenesis and regulation

Since their discovery in *Caenorhabditis elegans* a decade ago, miRNA have emerged as potent regulators of cellular physiology.^{57–59} miRNA are members of a growing class of noncoding RNA with functional relevance in a wide array of pathological conditions. miRNA biogenesis is a multiphase process, allowing for tight control over miRNA maturation and regulatory silencing.⁶⁰ In brief, miRNA are transcribed from introns or exons of noncoding RNA (or from introns of protein-coding RNA) by RNA polymerase II. These long hairpin pri-miRNA are then cleaved into ~70 nt pre-miRNA by Drosha (RNase III) before being exported from the nucleolus in an exportin-5-dependent manner. In the cytoplasm, pre-miRNA undergo final cleavage into ~22 nt, double-stranded, mature miRNA by the RNase III nuclease Dicer. One strand of the duplex is subsequently loaded into the RNA-induced silencing complex (RISC) in association with several argonaute-family proteins. Within this complex, miRNA bind to targets by complementary base pairing within the 3′ untranslated region (UTR) of mRNA. Target recognition hinges upon the 5′ seed region (nt 2–8) of each miRNA, though other factors contribute to target specificity,

many of which have yet to be fully described. Each miRNA has the potential to regulate hundreds of target mRNA, and thus may serve as key hubs of signaling and network regulation (Figure 1). As of publication, over 2,000 unique, mature miRNA have been identified within the human genome.⁶¹

The post-transcriptional repression of target mRNA by miRNA occurs in a cell- type- and tissue-specific manner, including within neurons and glia of the CNS.^{58,62,63} Disruption of miRNA biogenesis within neurons results in profound developmental impairment and deficits in neuronal differentiation, morphology, and signaling.^{64–66} miRNA have been shown to regulate a range of CNS functions, including reward feedback, circadian rhythmicity, and cognitive performance.^{67–69} Furthermore, the dysregulation of specific miRNA may contribute to a multitude of neuronal disorders, including schizophrenia, Alzheimer’s disease, autism, and bipolar disorder, among others.^{70–74} Hence, there is growing evidence for miRNA involvement in neuropathology, suggesting new avenues for therapeutic discovery.

The role of microRNA in depression

Could disruption of normal miRNA regulation result in a heightened susceptibility to clinical depression? Mutations within the target mRNA 3′ UTR, as well as within the miRNA itself, can result in impaired regulatory function. Likewise, even small changes in levels of miRNA expression can lead to both deviations from a homeostatic norm and profound molecular disruption. Aberrant biogenesis, shuttling, or regulatory binding of miRNA by Dicer, Drosha, RISC, or other processing proteins also has the potential to disrupt miRNA repression. Thus, there are multiple points at which disrupted miRNA signaling could initiate, or exacerbate, depressive pathophysiology.

Several miRNA–mRNA interactions have been found to be altered in animal models and in patients with clinical depression. A polymorphism within miR-30e is positively correlated with depression and its symptomatic onset.⁷⁵ miR-30e is a known tumor suppressor (via inhibition of cell growth) and is also associated with the development of schizophrenia.^{76,77} In addition, the mood stabilizers lithium and sodium valproate each modified the expression of a number of miRNA in Wistar rats.⁷⁸ Seven miRNAs were down-regulated in both treatment groups (let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, miR-221), with only miR-144 found to be up-regulated in both lithium- and valproate-treated animals. Collectively, these miRNA-target mRNAs are involved in PI 3-kinase, PKC, mitogen-activated protein kinase (MAPK), and immune response signaling pathways. Of note, electroconvulsive

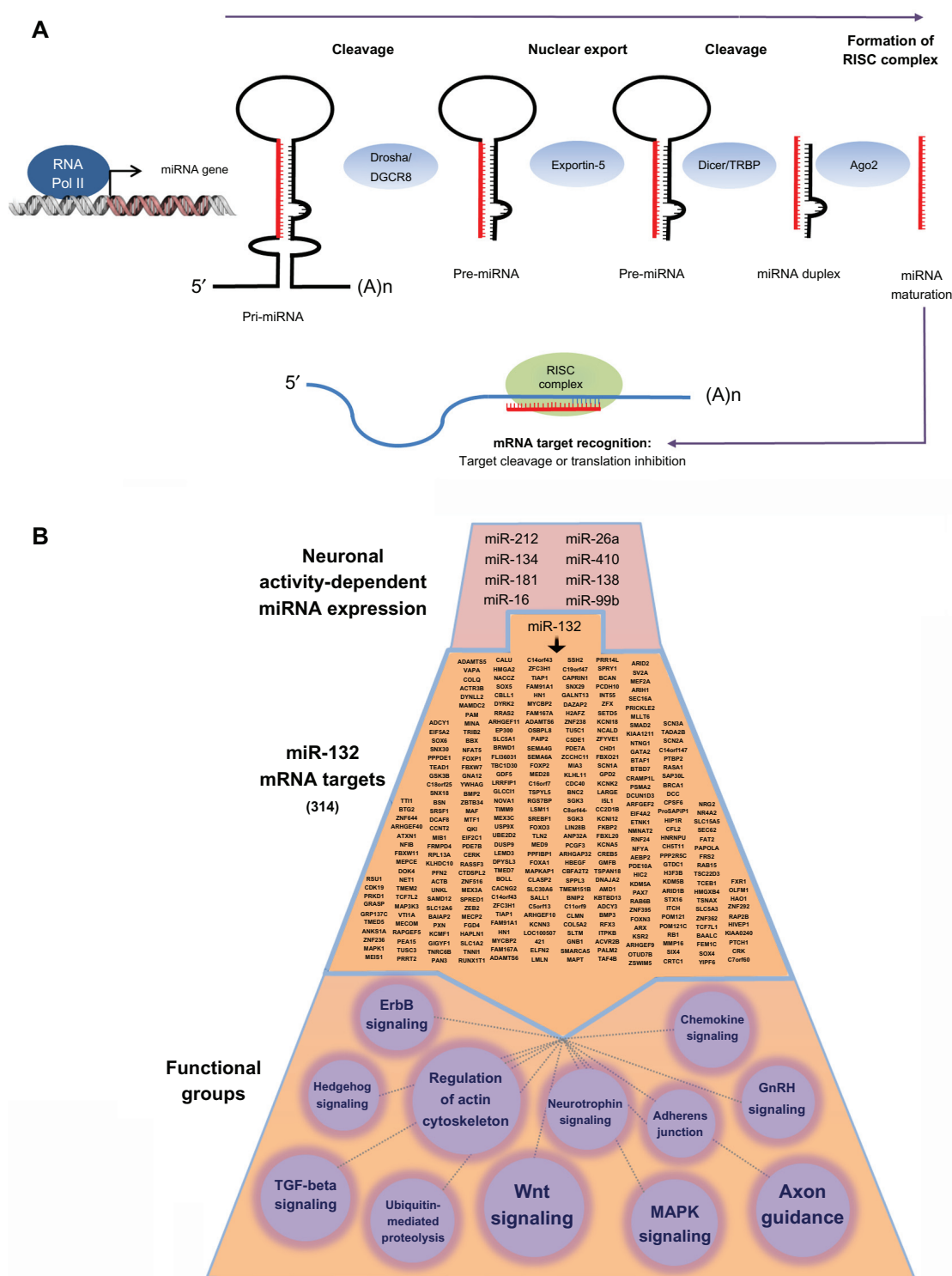


Figure 1 Biogenesis and miRNA functionality in neurons.

Notes: (A) miRNA are transcribed from noncoding regions of the genome by RNA polymerase II, forming a hairpin loop (pri-miRNA) that is cleaved by Drosha/DGCR8 into a ~70 nt pre-miRNA. Pre-miRNA are exported from the nucleus in an exportin-5-dependent manner before further processing by Dicer. The mature strand of the miRNA is loaded into the RISC complex, where it binds to its target mRNA to inhibit translation. (B) Depiction of the complexity of miRNA functionality. At the top of the panel, we provide a limited list of brain-enriched miRNA that are inducibly expressed by neuronal activity. To gain an appreciation of the functional effects of a single miRNA, we provide a list of miR-132 mRNA targets (314 in total; middle section). This list was generated using the TargetScan algorithm. KEGG pathways analysis (bottom section) was used to generate functional classifications of the miR132 targets. Only a subset of the classifications is provided here. Circle size denotes the relative number of genes that make up the classification (the smallest functional class is Hedgehog signaling, which comprises six genes).

Abbreviations: GnRH, gonadotropin-releasing hormone; KEGG, Kyoto Encyclopedia of Genes and Genomes; MAPK, mitogen-activated protein kinase; RNA, ribonucleic acid; mRNA, messenger RNA; miRNA, microRNA; nt, nucleotide; RISC, RNA-induced silencing complex; TGF, transforming growth factor; RNA pol II, RNA polymerase II; RISC, RNA-induced silencing complex; TAR, trans-activation response; TRBP, TAR RNA binding protein.

shock (ECS) is used as a therapy for the most severe cases of depression, and ECS-mediated neuronal activity induced 119 different miRNA within the hippocampus in animals.⁷⁹ Some global expression profiling of neuronal miRNA expression has been performed in the context of bipolar disorder, revealing several key alterations in miRNA expression.^{80,81} However, similar studies in major depression patients are only in their earliest stages.^{82,83} Hence, more such studies would provide needed insight into the differential expression of miRNA in patients with clinical depression.

MicroRNA in serotonergic signaling

miRNA may play a role in modulating depressive neurophysiology via the regulation of serotonergic signaling.⁸⁴ For example, miR-16 has been shown to target the serotonin transporter, SERT.^{85,86} As described above, SERT is the predominant mediator of SSRI antidepressants, and, as such, its regulation by miR-16 is of particular interest. Indeed, Wnt pathway-dependent increases in miR-16 within the raphe nuclei after treatment with fluoxetine (Prozac®; provided by Dr M Bouhassira, Eli Lilly, Indianapolis, IN, USA) suppressed SERT translation, leading to increased serotonergic activity and an antidepressive behavioral outcome.⁸⁶ Interestingly, evidence suggests that miR-16 is involved in fate determination of serotonergic and noradrenergic cells, the latter of which show increased miR-16 expression that suppresses translation of SERT mRNA within the locus coeruleus.⁸⁵ After fluoxetine treatment, cells within the locus coeruleus showed decreased miR-16 (in contrast to the effect within the raphe nuclei), illustrating the region-specific nature of SSRI treatment. In addition to serotonin transporters, several serotonin receptors are targets of miRNA. A polymorphism within the 3' UTR of the serotonergic 5-HT_{1B} receptor has been shown to prevent its down-regulation by miR-96, thus increasing receptor expression and membrane integration.⁸⁷ In addition, miR-195 regulates the 5-HT_{2A} serotonin receptor and potentially the 5-HT₄ receptor.^{70,88} Taken together, these studies suggest there are multiple means by which disruption of miRNA function could lead to an imbalance of serotonergic signaling, which could contribute to the multifaceted pathophysiology of clinical depression.

MicroRNA and the neurotrophic hypothesis of depression

While the above discussion of miRNA regulation of serotonergic signaling in models of depression reinforces the monoamine hypothesis, several other miRNA targets may

also influence depressive pathophysiology. BDNF is under the regulatory control of a number of miRNA, including miR-30a-5p whose expression increases in cells treated with the SSRI antidepressant drug paroxetine.⁸⁹⁻⁹¹ In addition to targeting the serotonin receptors mentioned above, miR-195 also targets BDNF and glutamate receptors.⁸⁸ Increases in BDNF are thought to indirectly mediate the antidepressant effects of SSRIs, so the over-expression of miRNA-targeting BDNF after drug treatment potentially suggests homeostatic feedback to maintain BDNF within a favorable range. Drugs that induce BDNF expression, without concordant increases in inhibitory miRNA, may prove to be more specific and efficient for antidepressant treatment than current antidepressants.

Expression of the neuronal plasticity-associated transcription factor CREB has also been reported to be reduced in the temporal cortex of depressed patients, while increases in CREB within the hippocampus yield an antidepressant effect.^{37,38,92} Indeed, SSRIs are known to increase CREB expression in an array of brain regions and to reverse the impairment in CREB function observed in animal models of depression.^{93,94} Several miRNA with increased expression in models of depression are predicted to target CREB, including miR-22, miR-200b, miR-211, and miR-300.⁹⁵ Of note, miR-124 is known to regulate serotonin-dependent synaptic plasticity by targeting CREB expression.⁹⁶ Given the role of CREB in neuronal plasticity and the neurotrophic hypothesis that prominently features downstream targets of BDNF, miRNAs associated with CREB-regulated transcription may serve as avenues for therapeutic investigation.

BDNF is known to contribute to a number of regulatory feedback loops within neurons, including one involving miR-132.⁹⁷⁻⁹⁹ miR-132 is induced by BDNF and is expressed in a CREB-dependent manner that couples synaptic activity to dendritic morphogenesis.^{89,100-103} miR-132 is also induced by light within the SCN, regulating the expression of the *per1* (*Period circadian protein homolog 1*) clock gene and modulating the capacity of light to entrain circadian rhythmicity.^{67,104} As described above, disruption of circadian timing is known to affect mood and depressive physiology. Thus, miR-132 regulates activity-dependent neuroplasticity as well as modulating sleep/wake cycles, both of which have the potential to affect depressive neurophysiology.

Circadian and stress-triggered dysregulation of miRNA regulation

In addition to miR-132, several other miRNA are involved in regulation of time. Indeed, interruption of miRNA biogenesis

disrupts circadian signaling, and numerous miRNA have been shown to oscillate in a diurnal manner.^{105,106} miR-219 expression is also regulated in a circadian-dependent manner through direct binding of Circadian Locomotor Output Cycles Kaput (CLOCK)/BMAL (Brain and muscle ARNT like 1) to its promoter region.⁶⁷ Other miRNA directly target components of the circadian clock-signaling pathway, such as the miR-192/194 cluster, which inhibits the PER gene family.¹⁰⁷ Of particular note, mutations within miR-182 increase vulnerability to depression, potentially as a subsequent symptom of sleep dysregulation.¹⁰⁸ miR-182 is predicted to target the circadian regulatory gene, *Clock*, and exhibits diurnal oscillation within the retina.^{106,108} Thus, miRNA may modulate the depressive effect of circadian disruption and could serve as therapeutic targets to restore normal sleep patterns and stabilize mood.

In addition to the miRNA response to sleep dysregulation, miRNA are involved in the cellular response to stress, which is a known trigger of clinical depression.^{109,110} Both acute and chronic stress alters miRNA expression within the amygdala and the hippocampus in a region-specific manner (eg, Let-7, miR-9, miR-26, miR-30, and miR-124, miR-132/212, miR-134, miR-183).^{111–114} Among these, miR-134 and miR-183 are both increased following acute stress, but are decreased and unchanged, respectively, after exposure to chronic stressors.¹¹¹ Both miRNA target splicing factor SC35, which promotes the processing of stress-induced acetylcholinesterase (AChE)-R rather than its more common variant (AChE-S).^{115,116} Thus, disruption of miR-134 and miR-183 expression would bias AChE RNA splicing toward a heightened stress response. Furthermore, excessive AChE-R is accompanied by over-expression of miR-132, which in turn suppresses translation of its target AChE-S, yielding cognitive impairment and disrupted nocturnal activity.¹¹⁷

Some measure of transcriptional regulation is expected as an adaptive response to stress, but excessive stress leads to dysfunction on a cellular and behavioral level. Prolonged or extreme stress can induce maladaptive glucocorticoid levels that contribute to oxidative stress and impaired neural function, all of which are commonly associated with depressive pathophysiology.¹¹⁸ miR-18 and miR-124a both down-regulate the glucocorticoid receptor, which also has the potential to be targeted by a range of other miRNA.^{119,120} Of note, glucocorticoid impairs miR-132 expression in a BDNF-dependent manner, suggesting a potential mechanism of stress-induced and miRNA-mediated depression.¹²¹ Together, these data indicate that antidepressant treatment has the capacity to reverse stress-induced changes to miRNA expression, which may serve to couple stress response

signaling with changes in neuronal plasticity.¹²² A list of depression-relevant miRNAs is included in Table 1.

MicroRNA as a target of depression therapy

The limitations of current monoaminergic-associated antidepressants suggest the need for alternative and/or more comprehensive approaches to the treatment of clinical depression. Given the multifaceted etiology of depression, novel therapeutics must take into account the many aspects of the molecular imbalances observed. The involvement of miRNA across many facets of depressive pathophysiology makes them intriguing targets of antidepressant treatment. miRNA may serve as fine-tuned homeostatic regulators that target multiple nodes of depressive dysfunction (Table 1). Given that some current antidepressants already modulate miRNA expression in a manner that is consistent with a beneficial effect, a more direct targeting of these miRNA may prove efficacious. Notably, the first phase II clinical trial involving miRNA is currently underway, with others not far behind.^{4,123–125} Indeed, the number of pharmaceutical companies with miRNA-based workflows is also on the rise (eg, MiRNA Therapeutics, Regulus, RXi Pharmaceuticals, Santaris).

As described in The role of microRNA in depression section, both increases and decreases in miRNA functionality are associated with depressive pathophysiology. miRNA over-expression leads to the inappropriate silencing of hundreds of downstream targets. The use of antisense or ‘sponge’ technology to bind specific nt sequences would selectively suppress the action of pathologically abundant miRNA.¹²⁶ As such, antagomirs (cholesterol-conjugated 2-*O*-methyl RNA antisense oligonucleotides) are currently being used to target aberrant miRNA expression in a range of disease models.^{123,127,128} Conversely, impairment of miRNA expression leads to excessive translation of target mRNA, detrimentally affecting neuronal physiology. While the lack of global miRNA dysregulation in models of clinical depression suggests that miRNA biogenesis and repression mechanisms remain largely intact, some mutations in genes required for miRNA processing have been found.¹²⁹ Further, mutations within specific miRNA promoters, seed sequences, or the 3' UTR of target mRNA may result in deficiency of regulation by specific miRNA. In the case of dysfunction with the miRNA itself, artificial miRNA mimetics may prove useful in restoring normal transcriptional regulation. The capacity of miRNA to maintain subtle regulatory balance is attractive in disorders where both increases and decreases of signaling activity can be causative.⁶⁸ In the case of excessive protein

Table 1 Depression-associated microRNAs

miRNA	Species	Relevant target(s)	Depression association/functional role	References
miR-30e	Human	Unknown	Polymorphism in depressed patients Tumor suppressor Inhibition of cell growth	74–76
miR-30a-5p	Human	BDNF	Increased expression after paroxetine treatment	87–89
let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, miR-221, miR-144	Rat	Diverse	Altered expression after lithium treatment PI-3-kinase, PKC, MAPK, and immune response signaling pathways	77
miR-16	Mouse	SERT	Serotonergic signaling Altered expression after fluoxetine treatment	83,84
miR-96	Human	5-HT1B receptor	Serotonergic signaling	85
miR-195	Human	5-HT2A receptor 5-HT4 receptor BDNF	Serotonergic signaling	86
miR-22, miR-200b, miR-211, and miR-300	Rat	CREB	Transcriptional regulation of neuronal plasticity and morphology	93
miR-124	Aplysia PI9 cells	CREB GCR	Modulates serotonin-dependent synaptic plasticity	94,117
miR-132	Mouse	p300 AChE	BDNF feedback loop, CREB-regulated, down-regulated by glucocorticoid, regulates neuronal morphology, circadian rhythmicity	66,95,98,99, 102,115,119
miR-219	Mouse	Unknown	CLOCK/BMAL-dependent circadian expression	66
miR-192/194	Cell culture	Period family	Modulation of circadian timing	105
miR-182	Mouse Human	<i>Clock</i>	Increases vulnerability to depression, circadian rhythmicity	104,106
miR-134, miR-183	Rat	SC35	Altered expression after stress, promote stress-induced AChE-R	109
miR-18	PI9 cells	GCR	Stress and depression	117

Abbreviations: AChE, acetylcholinesterase; ARNT, aryl hydrocarbon receptor nuclear translocator; AChE, acetylcholinesterase; BDNF, brain-derived neurotrophic factor; BMAL, brain and muscle ARNT like 1; CREB, cAMP response element-binding; CLOCK, Circadian Locomotor Output Cycles Kaput; GCR, glucocorticoid receptor; MAPK, mitogen-activated protein kinase; RNA, ribonucleic acid; miRNA, microRNA; PI-3, phosphoinositide 3; PKC, protein kinase C; SERT, serotonin transporter.

expression, custom small interfering RNA (siRNA) constructs can preferentially target specific protein-coding mRNA, even in the absence of endogenous miRNA regulation.¹³⁰ Indeed, the monoaminergic transporters DAT and SERT have both been effectively targeted using siRNA treatment, yielding an antidepressive effect.^{131–133}

Though the therapeutic potential of miRNA-based strategies is promising, significant challenges remain if the development of miRNA-mediated antidepressant therapy is to prove a meaningful endeavor. The capacity of miRNA to regulate multiple targets allows for therapeutic potential across several aspects of chemical imbalance, but caution must be taken to avoid unintended effects of altered miRNA expression. Small changes in miRNA activity can have an amplified effect on both direct and indirect downstream targets, many of which may be unrelated to the pathophysiology at hand. The involvement of miRNA in several signaling feedback loops, as well as their role in fine-tuning regulatory pathways, indicates the importance of careful dosing of

any miRNA-associated therapeutics.^{67,97} miRNA may have a buffered effect on downstream targets such that minor changes in miRNA expression therapeutically hone signaling pathways, but yield massive dysregulation if expressed beyond a threshold of tolerance.¹³⁴ Hence, each new treatment will require extensive toxicity screening due to the potential for multiple unintended miRNA effects.

The inability of nt constructs to cross the blood–brain barrier also remains problematic for therapeutic delivery. Indeed, many miRNA therapies currently under investigation in animal models employ highly invasive delivery methods that would be appropriate only in the most extreme cases of human disease. However, progress on this front is also being made with the use of adeno-associated viruses (AAVs) that have been shown to be a safe, and increasingly effective, means of gene delivery.^{135–137} Moreover, integration of viral-vector technology with the use of cell-type specific promoters could prove useful given the brain-region specific nature of molecular dysregulation in clinical depression (and indeed of miRNA themselves).⁸⁵

Despite these challenges, miRNA should remain a significant focus in the development of novel antidepressant treatments. Of great interest would be the additional use of high-throughput approaches to look at the global dysregulation of miRNA in animal models of depression, as well as in the post-mortem brains of depressed patients.⁸³ Some high-throughput screens of miRNA derived from the blood work of depressed patients has already taken place.^{82,138} Continuing to prioritize such studies would help identify potential miRNA biomarkers of clinical depression, and allow for screening of patient susceptibility. Similarly, profiling serum miRNA changes in patients with varying degrees of responsiveness to current antidepressants could help predict efficacy of treatment options for individuals. Such screens would allow for more informed, patient-driven treatments and reduce negative off-target effects. Such screens have found success in an array of disorders and thus hold promise for more accurately predicting patient vulnerability and resilience in clinical depression.^{139–142} Clearly, these applications may be more immediately attainable than the use of miRNA as direct therapeutics for clinical depression. The therapeutic application of the research findings mentioned here will require a more detailed understanding of the signaling networks that regulate, and are regulated by, miRNA in depressed patients. Nevertheless, miRNAs hold great potential in the treatment of clinical depression.

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Disclosure

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