Emerging role of microRNAs in major depressive disorder: diagnosis and therapeutic implications

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Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders. It affects about 17% of Americans during their lifetime and is associated with psychosocial impairment, poor quality of life, and significant disability, morbidity, and mortality. MDD is being diagnosed at early ages, and about 25% of people diagnosed with MDD are under 19 years old. Although much work has been done to characterize MDD, about 40% of MDD patients do not respond to the currently available medications. This is partially a result of poor understanding of the molecular pathophysiology underlying MDD.

As is well known, compromised neural and structural plasticity are intimately associated with MDD. This is evident from studies in MDD subjects showing altered structural and functional plasticity, changes in the synaptic circuitry, decreased dorsolateral prefrontal cortical activity, impaired synaptic connectivity between the frontal lobe and other brain regions, changes in number and shape of dendritic spines, the primary location of synapse formation, altered dendritic morphology of neurons in the hippocampus, decreased length and number of apical dendrites, neuronal atrophy and decreased volume of the hippocampus, etc.

Keywords: biomarker; depression; miRNA; neural plasticity; neurogenesis; stress

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The cellular mechanisms that underlie such compromised neural plasticity and structural impairments in MDD are not clearly understood, and no single mechanism appears to be responsible for its etiopathogenesis; however, it is becoming increasingly evident that MDD may result from disruptions across whole cellular networks, leading to aberrant information processing in the circuits that regulate mood, cognition, and neurovegetative functions. In fact, evidence demonstrating impaired cellular networks that regulate neural plasticity has reshaped our views about the neurobiological underpinnings of MDD.

In recent years, the emergence of small noncoding RNAs as a mega-controller and regulator of gene expression has gained much attention in various disease pathophysologies. These small noncoding RNAs regulate gene expression by several mechanisms, including ribosomal RNA modifications, repression of mRNA expression by RNA interference, alternative splicing, and regulatory mechanisms mediated by RNA-RNA interactions. The group of small noncoding RNAs include: miRNAs, small nucleolar RNAs, small interfering RNAs, piwi-interacting RNAs, splicedosomal RNAs, and p/MRP RNase genes. Among them, miRNAs are the most studied and well characterized; they have emerged as a major regulator of neural plasticity and higher brain functioning, regulate about 60% of total mammalian RNAs, and are involved in virtually all biological functions. By modulating translation and/or stability of mRNA targets in a coordinated and cohesive fashion, they are able to regulate entire genetic circuitries. It has been shown that a combination of miRNAs is a much more powerful regulator than individual miRNAs. Interestingly, differential coexpression of a group of miRNAs has not only been shown to play a direct role in human disease pathogenesis, but can also help in identifying the nature of disordered pathways implicated in such pathogenesis.

miRNAs are expressed highly in neurons, and because they can regulate the expression of a large number of target mRNAs, neuronal miRNA pathways can create an extremely powerful mechanism to dynamically adjust the protein content of neuronal compartments, even without the need for new gene transcription. miRNAs have been extensively studied in cancer biology; however, a large body of evidence demonstrates their role in several neuropsychiatric diseases, such as schizophrenia, autism, Parkinson’s disease, Huntington’s disease, Tourette’s syndrome, Fragile X syndrome, DiGeorge syndrome, Down syndrome, and Alzheimer’s disease. Studies are now being geared to examine if mutations in genes that encode miRNAs or various components of miRNA biogenesis machinery can lead to aberrant miRNA synthesis and target genes that can be linked to specific disease pathophysiology. Knowledge of the role of miRNAs in MDD is still in its infancy; however, several lines of evidence clearly demonstrate that miRNAs may play a major role in the development of stress-related disorders, including MDD. The aim of this review is to critically evaluate the role of miRNAs in MDD pathogenesis and examine whether miRNAs can be developed as biomarkers for depression.

miRNA biogenesis and regulation of target mRNA expression

An overview of miRNA biogenesis is depicted in Figure 1. As shown, miRNA biogenesis occurs in the nucleus. miRNAs are encoded within primary miRNA (pri-miRNA) gene transcripts that may be intergenic (away from known protein-coding genes) or may be located within introns of protein-coding host genes (intragenic).
miRNA genes are transcribed to long primary miRNA by RNA polymerase II or III. The pri-miRNAs are then processed further within the nucleus to form one or a series of small hairpin miRNA precursors, or precursor miRNAs (pre-miRNAs), that are generally 60 to 100 nt long and fold into a stem-loop structure. The protein that
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converts pri-miRNA into pre-miRNA is an RNase III enzyme, Drosha. Generally, Drosha requires the DiGeorge syndrome critical region 8 (DGCR8) protein as a cofactor for activation. Together with DGCR8, Drosha forms a large complex known as the “microprocessor complex.” Drosha removes the flanking segments and ~11 base pair (bp) stem region of the pri-miRNA. The pre-miRNAs are then transported out of the nucleus via the exportin transfer system, which consists of Exportin 5 and guanosine triphosphate-bound Ran (RanGTP). Pre-miRNA is released into the cytoplasm upon hydrolysis of GTP to GDP. The pre-miRNAs are further processed in the cytoplasm by the RNase III enzyme Dicer, which coverts pre-miRNA into double-stranded mature small RNA (miRNA/miRNA* duplexes) of approximately 22 nucleotides (nt) long. Dicer requires cofactors such as HIV-1 transactivating response (TAR) RNA–binding protein (TRBP) or protein kinase R (PKR)–activating protein (PACT). One of the miRNA/miRNA* duplexes is loaded onto an Argonaute (Ago) homologue protein (isoform of the eukaryotic translation initiation factor [eIF] 2C) to generate the effector complex, known as RNA-induced silencing complex (RISC). The other miRNA* strand is degraded.

**miRNA-mediated regulation of target mRNAs and expression**

RISC binds to specific “short-seed” sequences located predominantly within the 3’ untranslated region (3’ UTR) of target mRNAs, and can interfere with the translation of mRNA and/or reduce mRNA levels. miRNA-mediated translational inhibition also depends upon the 5’ cap region of the target mRNA. Ago proteins can stimulate miRNA-dependent translation inhibition by competing with eIF4E for the 5’ cap binding site, thus preventing circularization of mRNA and lowering initiation efficiency. Although miRNAs target transcripts through imperfect base-pairing to multiple sites in 3’ UTRs, Watson-Crick base-pairing to the 5’ end of miRNAs, especially to the so-called “seed” that comprises nucleotides 2 to 7, is also crucial for targeting. This provides a mechanism by which one miRNA can target several mRNAs. RISC can also associate with both the 60S ribosome and eIF6. eIF6 regulates the formation of the translationally active 80S subunit. By regulating eIF6, miRNAs can modify polysome formation and expose target mRNAs for degradation. In addition to the direct sequence-specific interaction of RISC with mRNAs, other proteins that bind nearby sites within the 3’ UTR (eg, fragile X mental retardation protein [FMRP] homologues, Hu protein B [HuB] family members, and other adenylate-uridylate–rich element [ARE]–binding proteins) may control the magnitude and even the direction of miRNA effects. In certain circumstances (eg, depending on the phase of the cell cycle in dividing cells, which possibly reflects reversible phosphorylation or methylation of FMRP homologues), miRNAs may actually enhance, rather than inhibit, translation.

miRNA-mediated regulation of mRNA stability is another mechanism by which miRNAs suppress expression of specific mRNA. Using miR-125b and let-7 as representative miRNAs, Wu et al showed that in mammalian cells the reduction in mRNA abundance is a consequence of accelerated deadenylation, which leads to rapid mRNA decay. Besides regulating translational processes, it has been shown that miRNA can also regulate gene transcription by targeting transcription factors. In this case, levels of transcription factors are downregulated by miRNAs, which in turn cause less expression of mRNA, leading to reduced protein synthesis.

Recent evidence suggests that miRNA biogenesis can be regulated at the epigenetic level. For example, inhibitors of DNA methylation and histone deacetylases can affect expression of several miRNAs. On the other hand, a subset of miRNAs can control the expression of epigenetic regulators, such as DNA methyltransferases, histone deacetylases, and polycomb group genes, leading to transcriptional activation of numerous protein coding gene sequences, thereby contributing to gene expression. This network of feedback between miRNAs and epigenetic pathways appears to form an epigenomics-miRNA regulatory circuit, and to organize the whole gene expression profile.

The expression of miRNAs is tissue-specific and, in some cases, even cell-type-specific. In addition, some of the miRNAs are expressed specifically at the developmental stages. Approximately 20% to 40% of miRNAs in the brain are developmentally regulated. For example, miR-124a, which is conserved at the nucleotide level and is important for neuronal differentiation, neurite outgrowth, and glucocorticoid receptor (GR)–mediated functions, is expressed throughout embryonic and adult brain. There are studies which
suggest that miRNAs, such as miR-124 and miR-128, are primarily expressed in neurons, whereas miR-23, miR-26, and miR-29 are expressed in high amounts in astrocytes. A recent study by He et al. suggests that a large number of miRNAs show distinct profiles in glutamatergic and GABAergic neurons and subtypes of GABAergic neurons. Even within neurons, it has been demonstrated that some of the pre-miRNAs are highly expressed in the dendrites where they can be locally transcribed into mature miRNAs and can locally regulate mRNA translation. These include synaptically enriched miRNAs: miR-200c, miR-339, miR-332, miR-318, miR-29a, miR-7, and miR-137. Several of the miRNAs are also expressed in the exons and presynaptic nerve terminals; some of them (miR-16, miR-221, miR-204, miR-15b) are highly expressed in distal axons compared with cell bodies. Moreover, a number of miRNAs encoded by a common pri-miRNA were differentially expressed in the distal axons, suggesting that there is a differential subcellular transport of miRNAs derived from the same coding region of the genome. Interestingly, the entire transcriptional machinery involved in the synthesis of mature miRNA has been shown to be localized in the synaptic fraction.

Given their differential nature of expression and because of the local regulation of mRNA translation, the role of miRNAs in numerous biological phenomena, including neuronal development, cell proliferation, cell cycle, neurogenesis, synaptic development, axon guidance, and neuronal plasticity, have been studied. miRNAs: potential regulators of neurogenesis and neural plasticity

miRNAs in neurogenesis

Adult neurogenesis, the process of generating new neurons from neural stem cells, plays a critical role in synaptic plasticity, learning and memory, and mood regulation. In the mammalian brain, neurogenesis occurs throughout adulthood in the hippocampus (subgranular zone [SGZ] of the dentate gyrus) and olfactory bulb (subventricular zone [SVZ]). Neurogenesis in the SVZ is important for olfactory learning, whereas hippocampal neurogenesis is involved in memory and spatial learning. Numerous studies suggest that stress and MDD are associated with decreased hippocampal neurogenesis. Additionally, disturbed adult neurogenesis, possibly resulting in a malfunctioning of hippocampus, may contribute to cognitive deficits. Conversely, hippocampal neurogenesis buffers stress responses and depressive behavior. Enriched environment, exercise, electroconvulsive therapy, deep brain stimulation, and antidepressants increase hippocampal neurogenesis. The regulatory factors that control adult neurogenesis are currently under investigation; however, recent studies demonstrate that miRNAs play a role in both embryonic as well as adult neurogenesis. For example, Choi et al. demonstrated that olfactory tissues express more than 100 distinct miRNAs, the most abundant being the miR-124a and let-7 variants and the family of miR-200. To determine whether miRNAs are required during olfactory neuronal development, these investigators analyzed embryonic tissues in which Dicer function was specifically ablated in olfactory progenitor cells. They showed that the loss of miRNA function from olfactory progenitor cells produced no alterations in patterning. In contrast, they noted that terminal differentiation of the olfactory progenitor pool into mature olfactory neurons does not occur and that the olfactory precursor cell population is not maintained. Dicer depletion also impacts proliferation and cell death, migration, and differentiation during corticogenesis as assessed by McLoughlin et al. in the developing brain. Using markers for proliferation and in vivo labeling, they showed reduced numbers of proliferating cells, altered cell cycle kinetics from embryonic day 15.5 (E15.5), distributed progenitor cells throughout the cortex (rather than restricted to the SVZ and ventricular zones), and increased cortical cell death as early as E15.5. DGC8 heterozygous mice also show reduced cell proliferation and neurogenesis in adult hippocampus. Pathania et al. recently showed that timely directed overexpression of miR-132 at the onset of synaptic integration using an inducible approach leads to a significant increase in the survival of newborn neurons in SVZ. These effects are mirrored with respective changes in the frequency of γ-aminobutyric acid (GABA)ergic and glutamatergic synaptic inputs reflecting altered synaptic integration. The results suggest that miR-132 forms the basis of a structural plasticity program seen in SVZ-olfactory bulb postnatal neurogenesis. Cheng et al. showed that miR-124 is an important regulator of the temporal progression of adult neurogenesis. They found that knockdown of endogenous miR-124 maintained purified SVZ stem cells as dividing precursors, whereas ectopic expression...
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led to precocious and increased neuron formation in mice. They identified the SRY-box transcription factor Sox9 as a physiological target of miR-124 during the transition from the transit-amplifying cell to the neuroblast stage. The overexpression of Sox9 abolished neuronal differentiation, whereas Sox9 knockdown led to increased neuron formation. Thus, miR-124–mediated repression of Sox9 is important for progression along the SVZ stem cell lineage to neurons. Bruno et al. identified brain-specific miRNA: miR-128, that represses nonsense–mediated RNA decay machinery, which controls transcripts of a battery of target genes to regulate neurogenesis and neural differentiation. More recently, Åkerblom et al. using a transgenic reporter mouse, found that miR-124 expression is initiated in the rapidly amplifying progenitors and remains expressed in the resulting neurons. Inhibition of miR-124 in vivo results in the blockade of neurogenesis, leading to the appearance of ectopic cells with astrocyte characteristics in the olfactory bulb. Conversely, neural stem cells are not maintained in the SVZ, when miR-124 is overexpressed, resulting in a loss of neurogenesis. These results suggest that miR-124 is a neuronal fate determinant in the SVZ. miR-137, which is epigenetically regulated by DNA methyl-CpG–binding protein, can modulate proliferation and differentiation of adult neural stem cells such that overexpression of miR-137 promotes, whereas its reduction enhances proliferation of adult neural stem cells. Recently, Zhang et al. identified a new cerebellum-enriched rno-miR-592, which plays an important role in embryonic neurogenesis and/or astrogliogenesis. By using gain-/loss-of-function approaches, they demonstrated that rno-miR-592 could change the balance between neuron- and astrocyte-like differentiation and neuronal morphology. miR-592 could induce astrogliogenesis differentiation arrest and/or enhance neurogenesis in vitro, whereas silencing of miR-592 was not beneficial for neuronal maturation. They also identified LRRC4C and NFASC as miR-592 target genes, suggesting that these two target genes may be involved in miR-592 regulative function in neuronal progenitor cell differentiation and neuronal maturation.

miRNAs in neural plasticity

As mentioned earlier, miRNAs play a critical role in regulating synaptic and neural plasticity. It has been shown that by knocking down components of the miRNA synthesis machinery such as Dicer leads to a reduction in neuronal size and branching as well as aberrant axonal pathfinding. On the other hand, DGCR8 knockout mice show loss of synaptic connectivity and reduced number and size of the dendritic spines. At the behavioral level, these mice display impaired spatial working memory–dependent tasks. FMRP, which regulates protein synthesis in dendritic spines after binding to specific sites within the 3’UTR of certain mRNAs in concert with RISC components Ago1 and Dicer, is associated with learning, and LTP. Both FMRP and RISC complex components are localized in the somatodendritic compartment and FMRP associates strongly with several components of the miRNA machinery, including mature miRNAs, pre-miRNAs, Dicer, and eIF2c. One of the RISC proteins, armitage, is essential for LTP and synaptic protein synthesis and is cleaved during the learning process. FMRP is also associated with miR-125b and miR-132 in the brain. miR-132 overexpression increases dendritic protrusion as well as branching, whereas miR-125b targets NR2A mRNA and regulates synaptic plasticity in a negative fashion. Similar negative regulation of the size of dendritic spines in rat hippocampal neurons has been shown to be associated with miR-138 as well as miR-134. miR-138 controls the expression of acyl-protein thioesterase 1 (APT1), an enzyme regulating the palmitoylation status of proteins that are known to function at the synapse. On the other hand, miR-134 inhibits translation of Lim-domain–containing protein kinase 1 (Limk1), a protein that regulates dendritic spine growth. Exposure to brain-derived neurotrophic factor (BDNF) relieves Limk1 translation suppression caused by miR-134. miR-134 can also promote dendri-togenesis by inhibiting the translational repressor Pumilio 2. Interestingly, BDNF is lower in the brain of depressed subjects. Recently, Cohen et al. showed that miR-485 regulates dendritic spine number in an activity-dependent manner, in conjunction with synaptic vesicle protein SV2A. miRISC protein Mov 10, an RNA helicase that associates with the Argonaute protein, is present at synapses and regulates synaptic expression of calmodulin (CaM) kinase II and Limk1.

Several studies demonstrate that Creb, a key transcription factor regulating synaptic plasticity and whose expression is lower in specific brain regions of MDD subjects, is one of the major targets of a number of miRNAs. Conversely, many miRNAs have binding sites in their promoter regions for Creb. Expression of
miR-132, which enhances neurite outgrowth, dendritic morphogenesis, and spine formation, is induced by BDNF via Creb. Another miRNA, miR-124, which plays a critical role in maintaining neuronal cell identity, is a major target of Creb. Interestingly, miR-124 is rapidly and robustly regulated by serotonin, which selectively affects mature miR-124 levels, without affecting its precursor, suggesting that the miR-124 level may be regulated during Dicer processing or RISC incorporation and stabilization. miR-124 responds to serotonin by de-repressing Creb and thereby enhances serotonin-dependent long-term facilitation. More recently, it has been shown that expression of SIRT1, which modulates synaptic plasticity and memory formation, is regulated via Creb, which itself is translationally repressed by miR-124. On the other hand, SIRT1 inhibits the expression of miR-134 via a repressor complex containing the transcription factor YY1. Unchecked miR-134 expression after SIRT1 deficiency may result in reduced expression of Creb and BDNF, whereas knocking down miR-134 rescues LTP and memory impairment caused by SIRT1 deficiency.

Impey et al have shown that CREB- and activity-regulated miR-132 is necessary and sufficient for hippocampal spine formation. Expression of the miR-132 target, p250GAP, is inversely correlated with miR-132 levels and spinogenesis. Furthermore, knockdown of p250GAP increases spine formation while introduction of a p250GAP mutant that is unresponsive to miR-132 attenuates this activity. Inhibition of miR-132 decreases both miniature excitatory postsynaptic current (mEPSC) frequency and the number of glutamate receptor 1 (GluR1)-positive spines, while knockdown of p250GAP has the opposite effect. Additionally, the miR-132/p250GAP circuit regulates Ras-related C3 botulinum toxin substrate 1 (Rac1) activity and spine formation by modulating synapse-specific Kalirin7-Rac1 signaling. These results suggest that neuronal activity regulates spine formation, in part, by increasing transcription of miR-132, which in turn activates a Rac1-Pak actin remodeling pathway. Behaviorally, it has been shown that overexpression of miR-132 in the rat perihinal cortex impairs short-term recognition memory, which is associated with a reduction in both long-term depression and long-term potentiation, and could be predicted from the excitatory and dendritogenic effects of mir132.

Long-lasting changes at synapses are at the core of brain activities, which primarily rely on enduring changes in synaptic efficacy. Such synaptic efficacy is critically dependent upon the regulation of specific protein synthesis near or within the synapse. In this regard, miRNAs provide fascinating mechanisms to modulate synaptic efficacy and plasticity by regulating translational control of protein synthesis locally at the synapse. Lugli et al determined that there was a synaptic enrichment of miRNAs in mouse forebrain synaptosomes and found that significant subsets of forebrain-expressed miRNAs are highly enriched in synaptic fractions relative to total forebrain homogenate. These synaptic-enriched miRNAs were biologically distinct from synaptic-depleted miRNAs, both in their expression patterns (synaptic-enriched miRNAs are expressed predominantly in pyramidal neurons, whereas synaptic-depleted miRNAs tend to have widespread and abundant tissue expression) and in their evolutionary histories (synaptic-enriched miRNAs tend to be evolutionarily new and often mammalian-specific, whereas the synaptic-depleted miRNAs tend to be highly conserved across vertebrates). Interestingly, they found that the synaptic enrichment was not simply related to the specificity of miRNA expression within neurons, but they arise from precursors that are expressed in the synaptic fractions and associated tightly with postsynaptic density (PSD). Furthermore, the synaptic enrichment of miRNAs was related to structural features of their precursors, suggesting a basis by which pre- or pri-miRNA may be selectively and stably transported to dendrites. Since both Dicer and pre-RNAs are expressed in synaptic fractions and are strongly associated with PSD, it suggests that at least a portion of the mature miRNAs are locally processed near synapses. Dicer is released from PSD and its RNase III activity is markedly enhanced following stimuli such as N-methyl-D-aspartate (NMDA) that can cause an increase in local calcium and activation of calpain. Dicer is expressed in PSDs, but is enzymatically inactive until conditions that activate calpain cause its liberation. These findings suggest that miRNAs are formed, at least in part, by the processing of miRNA precursors locally within dendritic spines, and synaptic stimulation may lead to local processing of miRNA precursors in proximity to the synapse. Synaptic efficacy can be regulated by modulating miRNA functions at the synapse and consequently synaptic plasticity due to the critical feature of miRNAs to regulate gene circuitry locally at the synapse in an activity-dependent fashion. This may provide a unique opportunity at the
therapeutic level, where regulation of miRNA can be used to control plasticity at the synapse.

**miRNAs in MDD pathogenesis and treatment**

The diagnostic and prognostic values of miRNA have been established in various types of cancer. The potential of miRNAs as diagnostic markers for psychiatric and neurodegenerative diseases has been advancing rapidly. Both preclinical and clinical evidence demonstrates that miRNAs can be extensively involved in stress-related disorders and MDD, as well as the antidepressant response.

**Coping response to stress and miRNAs**

An individual’s ability to cope with stress is critical in the development of MDD. We recently examined miRNA expression in both the frontal cortex of rats who developed behavior (learned helpless [LH]) that resembles stress-induced depression and those who did not develop depression (nonlearned helpless [NLH]), even though they received similar inescapable shocks (Table I). In this manner, we were able to distinguish the factors associated with the development of the depression phenotype. We found that NLH rats showed a robust adaptive miRNA response to inescapable shocks whereas LH rats showed a markedly blunted miRNA response. One set of miRNAs showed large, significant, and consistent alterations in NLH rats relative to tested controls (no shock group), and all showed a blunted response in LH rats (more like tested controls). These miRNAs were encoded at a few shared polycistronic loci, suggesting that their downregulation was coordinately controlled at the level of transcription. Most of these miRNAs have previously been shown to be enriched in synaptic fractions.

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**Table I.** miRNAs implicated in stress and depression.

| miRNAs                        | Effects                                                                 | References                       |
|-------------------------------|-------------------------------------------------------------------------|----------------------------------|
| Restraint stress              | Frontal cortex: miR-9, miR-9*, miR-26b, miR-29b, miR-30b, miR-30c, miR-30e, miR-125a, miR-126-3p, miR-129-3p, miR-207, miR-21, miR-351, miR-423, miR-487b, miR-494, miR-690, miR-691, miR-709, miR-711, and Let-7 a-e-let-7a, miR-9, miR-26a/b, miR-30b/c, miR-125a | Rinaldi et al.134                |
| Immobilization stress         | Hippocampus CA1, amygdala: miR-134, miR-183, miR-132, Let-7a-1, miR-9-1, miR-124a-1 | Meerson et al.136               |
| Unpredictable chronic mild stress | Hippocampus: miR298, miR130b, miR135a, miR323, miR503, miR15b, miR532, and miR125a and up-regulating miRNAs miR7a, miR212, miR124, miR139, miR182 | Cao et al.135                   |
| Early life stress             | Medial prefrontal cortex: pre-miRs 132, 124-1, 9-1, 9-3, 212, 29a       | Uchida et al.140                 |
| Animal model of depression    | Learned helpless vs control frontal cortex: mmu-miR-184, mmu-miR-197, mmu-miR-107, mmu-miR-329, mmu-miR-125a-5p, mmu-miR-872, mmu-miR-181c, mmu-miR-18a*, mmu-miR-29b*, mmu-let-7a*, mmu-let-7e*, mmu-let-20a* | Smallheiser et al.132          |
| Postmortem brain studies      | Prefrontal cortex: hsa-miR-142-5p, hsa-miR-33a, hsa-miR-137, hsa-miR-489, hsa-miR-148b, hsa-miR-101, hsa-miR-324-5p, hsa-miR-301a, hsa-miR-146a, hsa-miR-335, hsa-miR-494, hsa-miR-20b, hsa-miR-376a*, hsa-miR-190, hsa-miR-155, hsa-miR-660, hsa-miR-552, hsa-miR-453, hsa-miR-130a, hsa-miR-27a, hsa-miR-497, hsa-miR-10a, hsa-miR-20a, hsa-miR-142-3p | Smallheiser et al.133          |
| Peripheral mononuclear cells  | hsa-miR-107, hsa-miR-133a, hsa-miR-148a, hsa-miR-200c, hsa-miR-381, hsa-miR-425-3p, hsa-miR-494, hsa-miR-517b, hsa-miR-579, hsa-miR-589, hsa-miR-636, hsa-miR-652, hsa-miR-941, hsa-miR-1243 | Belzeaux et al.134             |
| Whole blood cells (12 weeks of treatment with escitalopram) | hsa-miR-130b, hsa-miR-505, hsa-miR-29b-2, hsa-miR-26b, hsa-miR-22, hsa-miR-26a, hsa-miR-664, hsa-miR-494, hsa-let-7d, hsa-let-7g, hsa-let-7e, hsa-miR-34c-5p, hsa-let-7f, hsa-miR-629, hsa-miR-106b, hsa-miR-103, hsa-miR-191, hsa-miR-128, hsa-miR-302-3p, hsa-miR-374b, hsa-miR-132, hsa-miR-30d, hsa-miR-770-5p, hsa-miR-589, hsa-miR-183, hsa-miR-574-3p, hsa-miR-140-3p, hsa-miR-335, hsa-miR-361-5p | Bocchio-Chiavetto et al.135    |
mRNAs. Interestingly, half of this set are predicted to hit Creb1 as a target, and binding sites for CREB lie upstream of miR-96, miR-182, miR-183, miR-200a, miR-200b, miR-200c, miR-220a, and miR-200b. This suggests that a similar feedback loop arrangement may also exist for Creb, similar to what has been described for other Creb-stimulated miRNAs and target genes. Since these miRNAs are downregulated in NLH rats, but not LH rats, this can be interpreted as a homeostatic response intended to minimize the repressive effects on Creb1. In addition, we identified a large core coexpression module, consisting of miRNAs that are strongly correlated with each other across individuals of the LH group, but not with either the NLH or tested control group. The presence of such a module implies that the normal homeostatic miRNA response to repeated inescapable shock is not merely absent or blunted in LH rats; rather, gene expression networks are actively reorganized in LH rats, which may support their distinctive persistent phenotype.

Another piece of evidence comes from studies of stress-sensitive F344 rats (which show a higher stress response to restraint stress) compared with Sprague-Dawley rats (which show lower hypothalamic-pituitary adrenal axis activity over a period of time). In this context, it is important to mention that glucocorticoids regulate the hypothalamic-pituitary adrenal axis through a negative feedback mechanism while binding to soluble GRs in the pituitary and the hypothalamus and inhibit the release of corticotropin-releasing factor and adrenocorticotropic hormone. Several studies have reported that the GR expression of is downregulated in depressed individuals. The GR protein is under constant miRNA regulation. More specifically, miR-124a and miR-18a bind to the 3' UTR of GR and downregulate its expression. Overexpression of miR-18a attenuates the glucocorticoid-induced leucine zipper, a gene induced by stress-like levels of glucocorticoid. It is possible that higher expression of miR-18a and consequent downregulation of GR could be responsible for the genetic susceptibility to stress in F344 rats. Turner et al recently predicted several possible miRNA binding sites within the GR first exon, suggesting further regulation of GR genes by miRNAs.

**miRNAs in response to stress**

Several types of stressors have been utilized to examine how miRNAs respond to stressors. Interestingly, acute and chronic restrained stress cause differential changes in miRNA expression in a brain region-specific manner (Table I). For example, acute stress induces a transient increase in the expression of selected miRNAs (miR-9, miR-9*, miR-26b, miR-29b, miR-30b, miR-30c, miR-30e, miR-125a, miR-126-3p, miR-129-5p, miR-207, miR-212, miR-351, miR-423, miR-487b, miR-494, miR-690, miR-691, miR-709, miR-711, and Let-7 a-e) in the frontal cortex, but not the hippocampus. Some of them (let-7a, miR-9, miR-26a/b, miR-30b/c, and miR-125a) show an increase in their expression 5 days after acute stress; however, their expression levels are not altered after repeated restraint. These results suggest that acute stress modulates miRNA expression quickly to external stimuli by changing their synaptic efficacy through regulation of localized mRNA translation.
Using unpredictable chronic mild stress combined with separation, Cao et al. found changes in 13 specific miRNAs in the rat hippocampus (Table I). These include downregulating miRNAs (miR298, miR-130b, miR-135a, miR-323, miR-503, miR-15b, miR-532, and miR-125a) and upregulating miRNAs (miR7a, miR-212, miR-124, miR-139, and miR-182). Among these, miR-125a and miR-182 recovered to normal after intervention with traditional herbal antidepressant medication.

The effect of early-life stress, which is one of the critical factors in the development of affective disorders, on miRNA expression, has also been studied. Uchida et al. found that maternal separation enhanced stress vulnerability to repeated restraint stress exposure in adulthood (Table I). At the molecular level, maternal separation increased the expression of repressor element–1 silencing transcription factor (REST) 4. Transient overexpression of REST4 in the medial prefrontal cortex of neonatal mice produced depression-like behaviors in adults after repeated exposure to restraint stress, suggesting that REST4 may play a role in the development of stress vulnerability. REST regulates the expression of several miRNAs that are involved in brain development and plasticity. For example, maternal separation increased the expression of REST-associated premiRs 132, 124-1, 9-1, 9-3, 212, and 29a in rat medial prefrontal cortex. miR-132 and miR-124 are involved in synaptic plasticity and cause decreased dendritic length, high synaptic density, and altered basal neuronal activity. Interestingly, Bai et al. demonstrated that maternal deprivation not only led to the development of depressive behavior in rats and a subsequent decrease in BDNF expression, but decreased BDNF expression was negatively correlated with the expression of miR-16. miR-16 has been shown to be an important effector of antidepressant action in serotonergic raphe and noradrenergic locus coeruleus as well as adult neurogenesis in the hippocampus.

miRNAs and antidepressants

Several recent studies show that miRNAs may be involved in the mechanisms of action of antidepressants. Baudry et al. showed that the serotonin transporter is a target of miR-16, which has a higher expression pattern in noradrenergic neurons than in serotonergic neurons. A reduction of miR-16 in noradrenergic neurons caused de novo serotonin transporter expression. Interestingly, long-term treatment with fluoxetine to mice increased miR-16 levels in serotonergic raphe nuclei, which, in turn, reduced serotonin transporter expression. Furthermore, raphe responded to long-term fluoxetine treatment by releasing S100β, which, in turn, acted on the noradrenergic neurons of the coeruleus locus. Thus, by lowering miR-16 levels, S100β unlocked the expression of serotoninergic functions in the noradrenergic brain area. This study suggests that miR-16 acts as a central effector in regulating serotonin transporter expression and mediates the adaptive response of serotonergic and noradrenergic neurons to fluoxetine treatment. These investigators further showed that fluoxetine treatment induced the secretion of various signaling molecules such as BDNF, Wnt2, and 15d-PGJ2 from raphe serotoninergic neurons and acted cooperatively on the hippocampus, whereas S100β controlled the locus coeruleus-dependent hippocampal response to fluoxetine. These signals relayed the action of fluoxetine on adult hippocampal neurogenesis by down-regulating miR-16 in the hippocampus in a region-specific manner. In a complementary fashion, these signaling molecules were found to be increased in the cerebrospinal fluid of depressed patients upon fluoxetine treatment.

O’Connor et al. investigated whether early-life stress in rats induced changes in hippocampal miRNA levels and whether the rapidly acting NMDA receptor antagonist ketamine, electroconvulsive therapy (ECT), or fluoxetine treatment could reverse these changes. They found that early-life stress affected expression of multiple hippocampal miRNAs. Antidepressant treatments reversed some of these effects including a stress-induced change to miR-451. Ketamine and ECT possess the highest number of common targets, suggesting convergence on common pathways. Interestingly, all three treatments possessed miR-598-5p as a common target. This demonstrates that changes to hippocampal miRNA expression may represent an important component of stress-induced pathology, and antidepressant action may reverse these. In this context, Ryan et al. examined ECT-induced BDNF expression and BDNF-associated miRNAs. Following acute or chronic electroconvulsive stimulation (ECS), they found that the level of selective miR-212 was significantly increased in dentate gyrus. miR-212 level was also increased in parallel in whole blood following chronic ECS and was positively correlated with miR-212 level in the dentate gyrus, sug-
gesting that miR-212 may be crucial in the mechanism of action of ECT and that it can be used as a biomarker.

Using genome-wide expression profiling of human lymphoblastoid cell lines (LCLs), Morag et al\(^\text{155}\) identified CHL1 as a selective serotonin reuptake inhibitor (SSRI) sensitivity biomarker. The same group reported that specific miRNAs may be implicated in SSRI sensitivity of LCLs.\(^\text{156}\) They examined genome-wide expression profiling with miRNAs in LCLs exhibiting high or low sensitivities to paroxetine. They found that miR-151-3p had a 6.7-fold higher basal expression in paroxetine-sensitive LCLs, which was correlated with lower expression of CHL1, a target of miR-151-3p. The additional miRNAs miR-212, miR-132, miR-30b*, let-7b, and let-7c also differed by >1.5-fold between the two LCL groups. These results suggest a possible therapeutic value of miRNAs in responders vs nonresponders to antidepressant treatment in MDD patients.

Schmidt et al\(^\text{157}\) found that the therapeutic action of fluoxetine is associated with a reduction in prefrontal cortical mir-1971 expression levels in a mouse model of post-traumatic stress disorder. Long-term lithium and valproate treatment have also been shown to alter a number of miRNAs; however, 9 miRNAs (let-7b, let-7c, miR-105, miR-128a, miR-24a, miR-30c, miR-34a, miR-221, and miR-144) were regulated by both lithium and valproate. The most significant signaling pathways that are targeted by these miRNAs are the PKC, PTEN, ERK-MAP kinase, Wnt/β-catenin, and β-adrenergic pathways. Intriguingly, four different downregulated miRNAs were encoded at chromosomal loci near other miRNAs and are possibly transcribed by the same pri-miRNA gene transcripts (mir-142-5p and 142-3p; mir-494, 376a*, 496, and 369-3p; mir-23b, 27b and 24-1*; mir-34b* and 34c; mir-17* and 20a). In addition, three pairs of miRNAs were encoded at distances greater than 100 kb, but still lie within the same chromosomal region (mir-424 and 20b at Xq26.2-3, 377 kb apart; mir-142 and 301a at 17q22, 820 kb apart; mir-324-5p and 497 at 17p13.1, 205 kb apart). This suggests that at least some of the downregulated miRNA expression is due to decreased transcription. Many of the downregulated miRNAs also shared 5’ seed sequences that are involved in target recognition. For example, identical seed sequences are shared by: (i) mir-20a and 20b; (ii) mir-301a and 130a; and (iii) mir-424 and 497. In addition, a 6-mer nucleotide motif is shared by mir-34a, 34b*, and 34c, and strikingly, a 5-mer motif (AGUGC) within the 5’ seed is shared by 5 of the affected miRNAs (mir-148b, 301a, 130a, 20a, and 20b) that is predicted to bind Alu sequences within the 3’ UTR region of target mRNAs. This suggests that the downregulated miRNAs should exhibit extensive overlap among their mRNA targets. When we did pair-wise correlation (a complementary method of analyzing the miRNA expression data to identify pairs of miRNAs that are coregulated in their expression, up or down, across individuals within a single group) we found that a set of 29 miRNAs, none of whom were pairwise correlated in the normal control group, formed a very extensive interconnected network in the MDD group. Several of the miRNAs (let-7b, mir-132, 181b, 338-3p, 486-5p, and 650) were “hubs” correlated with four to nine other miRNAs in the network. Target analysis revealed that many of the targets are transcription factors, and nuclear, transmembrane, and signaling proteins. Intriguingly, four different downregulated miRNAs target VEGFA (mir-20b, 20a, 34a, and 34b*), a molecule implicated in depression in both humans and animal models. Other validated targets include BCL2 (mir-34a), DNMT3B (mir-148b), and MYCN (mir-101, 34a). Among predicted targets, estrogen receptor α, ESR1, was predicted to be targeted by three different down-regulated miRNAs (mir-148b, 301a, 496). Others targeted by three or more affected

**miRNAs in MDD subjects**

One of the approaches that have been taken to directly assess the status of miRNAs in psychiatric illnesses is to examine the postmortem brain. Using this approach, we recently profiled miRNA expression in the prefrontal cortex of depressed subjects who had died by suicide (Table I).\(^\text{158}\) We took several different approaches to analyzing the data. When we analyzed miRNA expression globally, we found that 21 miRNAs were significantly downregulated in the MDD group. We also found that 24 miRNAs were downregulated by 30% (although not statistically significant), suggesting a global downregulation of miRNA levels in the MDD group. When analyzed individually, we found that almost half of the downregulated miRNAs were encoded at chromosomal loci near other miRNAs and are possibly transcribed by the same pri-miRNA gene transcripts (mir-142-5p and 142-3p; mir-494, 376a*, 496, and 369-3p; mir-23b, 27b and 24-1*; mir-34b* and 34c; mir-17* and 20a). In addition, three pairs of miRNAs were encoded at distances greater than 100 kb, but still lie within the same chromosomal region (mir-424 and 20b at Xq26.2-3, 377 kb apart; mir-142 and 301a at 17q22, 820 kb apart; mir-324-5p and 497 at 17p13.1, 205 kb apart). This suggests that at least some of the downregulated miRNA expression is due to decreased transcription. Many of the downregulated miRNAs also shared 5’ seed sequences that are involved in target recognition. For example, identical seed sequences are shared by: (i) mir-20a and 20b; (ii) mir-301a and 130a; and (iii) mir-424 and 497. In addition, a 6-mer nucleotide motif is shared by mir-34a, 34b*, and 34c, and strikingly, a 5-mer motif (AGUGC) within the 5’ seed is shared by 5 of the affected miRNAs (mir-148b, 301a, 130a, 20a, and 20b) that is predicted to bind Alu sequences within the 3’ UTR region of target mRNAs. This suggests that the downregulated miRNAs should exhibit extensive overlap among their mRNA targets. When we did pair-wise correlation (a complementary method of analyzing the miRNA expression data to identify pairs of miRNAs that are coregulated in their expression, up or down, across individuals within a single group) we found that a set of 29 miRNAs, none of whom were pairwise correlated in the normal control group, formed a very extensive interconnected network in the MDD group. Several of the miRNAs (let-7b, mir-132, 181b, 338-3p, 486-5p, and 650) were “hubs” correlated with four to nine other miRNAs in the network. Target analysis revealed that many of the targets are transcription factors, and nuclear, transmembrane, and signaling proteins. Intriguingly, four different downregulated miRNAs target VEGFA (mir-20b, 20a, 34a, and 34b*), a molecule implicated in depression in both humans and animal models. Other validated targets include BCL2 (mir-34a), DNMT3B (mir-148b), and MYCN (mir-101, 34a). Among predicted targets, estrogen receptor α, ESR1, was predicted to be targeted by three different down-regulated miRNAs (mir-148b, 301a, 496). Others targeted by three or more affected
miRNAs include ubiquitin ligases (UBE2D1 and UBE2W); signal transduction mediators (CAMK2G, AKAP1); the splicing factor NOVA1 that regulates brain-specific alternative splicing; the GABA-A receptor subunit GABRA4; calcium channel CACNA1C; and brain-active transcription factors including SMAD5, MITF, BACH2, MYCN, and ARID4A. Several of these predicted targets interact with validated targets; for example, ARIA4A binds E2F1; SMAD5 binds RUNX1; and estradiol treatment decreases E2F1 levels in the prefrontal cortex. BACH2 transcription factor binding sites have been identified upstream of many brain-expressed miRNAs. Retinoblastoma binding protein 1 (ARIA4A) is of interest because it recruits histone deacetylases and regulates gene expression via chromatin-based silencing.

Recently, He et al. studied an association between miRNA processing gene variants and depression. They genotyped three polymorphisms from three miRNA processing genes (DGCR8, AGO1, and GEMIN4) in a case-control study including 314 patients and 252 matched healthy controls. Frequencies of genotypes and alleles showed a significant difference between patients with depression and healthy controls in DGCR8 rs3757 and AGO1 rs636832. An allele frequency was significantly higher in rs3757 and lower in rs636832, respectively. Variant allele of DGCR8 rs3757 was associated with increased risk of suicidal tendency and improvement response to antidepressant treatment, whereas the variant of AGO1 rs636832 showed decreased risk of suicidal tendency, suicidal behavior, and recurrence. Besides, allele frequency showed significant difference when comparing patients with remission with controls; no significant differences were found in GEMIN4 rs7813 between patients and healthy controls. DGCR8 rs3757 and AGO1 rs636832 were found to have a significant association with depression, and GEMIN4 rs7813 did not affect susceptibility to depression. These observations suggested that miRNA processing polymorphisms may affect depression risk and treatment.

**Circulating miRNAs: potential biomarker in depression and antidepressant response**

miRNAs can be detected in circulating biological fluids such as serum, plasma, urine, saliva, and cerebrospinal fluid (CSF). Interestingly, it has been shown that miRNAs are endogenously expressed in plasma and their expression profile is similar in blood cells. More interestingly, under healthy conditions, these miRNAs are stably expressed in blood cells; however, under pathological conditions, the profile of miRNAs changes significantly, suggesting the possibility that peripheral miRNAs can be used as a reliable biomarker under disease conditions. Although the source of miRNAs in peripheral cells is not clear, it has been shown that miRNAs can be released actively or passively from tissues into the circulating blood. The actively secreted miRNAs are enclosed in exosomes and protected by RNA binding proteins including NPM1, HDL, or Argonaute2. Therefore, measuring miRNAs in blood cells is highly reproducible. Interestingly, it has been shown that exosomes containing miRNAs are excreted physiologically in response to stress or brain injury, suggesting that these miRNAs can be ideal biomarker candidates. Exosomal miRNAs are processed by the same machinery used in miRNA biogenesis and thus have widespread consequences within the cell by inhibiting the expression of target protein-coding genes.

Over the past several years, attempts have been put forward towards developing circulating miRNAs as a potential biomarker for many diseases. These include cancer and cardiovascular, inflammatory, and neurodegenerative diseases. In cancer patients, miRNAs have not only been shown to be useful indicators of various types of cancer, but based on miRNA profiling, it can be shown which patient group responds better to a particular treatment regimen. In neurological disorders, there is a significant correlation between circulating miRNAs and brain disease and injury. For example, miR-9 is decreased in blood cells, and in the cortex and hippocampus of Alzheimer’s disease patients. Similarly, circulating miR-34 serves as a novel biomarker for Huntington’s disease. Identifying biomarkers in these diseases has been a challenging task due to the heterogeneity and complex nature of psychiatric illnesses. Nonetheless, emerging studies provide evidence that miRNAs can be used successfully as biomarkers in these illnesses. For example, in schizophrenia patients, several circulating miRNAs (miR-181b, miR-219-2-3p, miR-1308, let-7g, and miR-195) have been identified as potential disease biomarkers. Plasma miR-134 levels in drug-free, 2-week medicated, and 4-week medicated bipolar mania patients were significantly decreased when compared with controls, and its level increased following medication. Decreased circulating miR-134
level, both in drug-free and medicated patients, showed a negative correlation with the clinical scales, suggesting that a decrease in plasma miR-134 levels may be directly associated with the pathophysiology and severity of manic symptoms in bipolar disorder.

The use of miRNAs as a peripheral biomarker in MDD is gaining momentum. Belzeaux et al examined miRNA expression profiles in peripheral blood mononuclear cells (PBMCs) collected from 16 severe MDD patients and 13 matched controls at baseline, and 2 and 8 weeks after treatment (Table I). A comparison of miRNA expression between MDD patients and controls at baseline and at 8 weeks showed a similar number of dysregulated miRNAs (14 miRNAs, with 9 miRNAs upregulated and 5 downregulated). miRNAs that showed changes between MDD and controls at base line included: has-miR-107, miR-133a, miR-148a, miR-200c, miR-381, miR-425-3p, miR-494, miR-517b, miR-579, miR-589, miR-636, miR-652, miR-941, and miR-1243. Only two miRNAs showed stable overexpression in MDD patients during the 8-week follow-up compared with controls (miR-941 and miR-589). They also identified miRNAs exhibiting significant variations of expression among patients with clinical improvement (7 upregulated and 1 downregulated). Fourteen dysregulated miRNAs had putative mRNA targets that were differentially expressed in MDD, suggesting that a common RNA regulatory network functions in MDD. These results suggest the potential utility of miRNA signatures as markers of major depressive episode evolution.

Bocchio-Chiavetto et al conducted a whole-miRNAome quantitative analysis in the blood of 10 MDD subjects after 12 weeks of treatment with escitalopram (Table I). They found that 30 miRNAs were differentially expressed after the escitalopram treatment: 28 miRNAs were upregulated, and two miRNAs were downregulated. Thirteen (let-7d, let-7e, miR-26a, miR-26b, miR-34c-5p, miR-103, miR-128, miR-132, miR-22) play a role in neural plasticity, neurogenesis, and stress response, and in the pathogenetic mechanisms of several neuropsychiatric diseases. miR-132 exerts critical functions in the biological circuits implicated in neurogenesis and synaptic plasticity, stimulating axonal and dendritic outgrowth in different brain areas. This miRNA, together with miR-26a, miR-26b, and miR-183, widely contributes to the action of the neurotrophin BDNF in the brain.

Conclusion and future directions

Based on studies showing the involvement of miRNAs in neural plasticity, neurogenesis, and stress response, it is clear that miRNAs may participate in the pathogenesis of MDD. More direct evidence comes from human postmortem brain studies showing aberrant expression of miRNAs in the prefrontal cortical area. From these, as well as animal studies showing a blunted response in NLH rats, one can assume that miRNAs may actively participate in developing the MDD phenotype.

Despite these findings, one needs to find an integrated view of miRNA networks and the pathways that are affected by these miRNAs. It is well established that a combination of miRNAs is a much more powerful regulator than individual miRNAs. Interestingly, differential c-expression of a group of miRNAs has not only been shown to play a direct role in human disease pathogenesis, but they also help in identifying the nature of disordered pathways implicated in such pathogenesis. A set of miRNAs that are significantly affected in MDD, and the corresponding set of mRNAs that are affected in the same samples, will help resolve this issue. The affected miRNAs and mRNAs are likely to interact with and regulate each other, either directly as targets or indirectly as part of larger regulatory networks. One can also identify sets of miRNAs that are not correlated in expression across individuals in the control group, yet are positively correlated in the MDD group and vice versa. There is a
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effective phosphorylation of eIF2C appears to be due to activation of ERK1/2. Since we have shown abnormalities in calcium-sensing proteins and ERK1/2 signaling in the brain of MDD subjects, it will be worthwhile to ask whether Dicer cleavage patterns or eIF2C phosphorylation are altered in the MDD group. One can also examine whether there is any genetic link between mRNA and MDD. Such genetic linkage has been reported in specific miRNAs in schizophrenia.

The development of miRNAs as biomarkers for MDD pathogenesis will be an important step in detecting MDD pathogenesis. In this regard, blood cell studies will be critical. The miRNA findings in these cells of MDD subjects so far have been very exciting, and indicate the possibility of developing biomarkers in a non-invasive manner. Also, the blood expressed miRNAs can be expanded to monitor antidepressant response. Much work, however, is needed in this direction, since miRNAs may be expressed differently in various blood cell types. In addition, whether miRNAs in a specific blood cell type truly represent brain-derived miRNAs, is unclear at the present time. In this regard, measuring miRNAs in exosomes may be an alternate and better approach.

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Nuevo papel de los microARNs en el trastorno depresivo mayor: consecuencias diagnósticas y terapéuticas

El episodio depresivo caracterizado (EDC) es un problema de salud pública. Malgré des progrès significatifs, les mécanismes pathogènes associés à l’EDC restent obscurs. De plus, un nombre significatif de personnes atteintes d’EDC ne répond pas à la traitements actuellement disponibles. Les microARN (miARNs) sont une classe de ARNs petits non codants qui contrôlent l’expression génique à la moduler la traduction, la dégradation de l’ARN messager (ARNm) ou la stabilité des cibles de l’ARNm. La connaissance du rôle des miARN dans la physiopathologie des maladies prend rapidement de l’essor. Des études récentes démontrant l’impli- cation des miARN dans plusieurs aspects de plasticité neuronale, de neurogénese, de réponse au stress et d’études plus directes dans le cerveau humain postmortem affirment que les miARN non seulement jouent un rôle décisif dans la pathoge- nèse de l’EDC, mais qu’ils peuvent aussi inaugurer de nouvelles voies pour le développement de cibles thérapeutiques. Les miARN circulants sont mainte- nant considérés comme des biomarqueurs possibles dans la pathogenèse de la maladie et dans les réponses thérapeutiques de contrôle à cause de la présence et/ou de la libération des miARN dans les cellules sanguines comme dans d’autres tissus périphériques. Nous analysons dans cet article ces diffé- rents aspects de façon complète et critique.

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