Biomarkers in Neuropsychiatry 5 (2021) 100035

Contents lists available at ScienceDirect

Biomarkers in Neuropsychiatry

journal homepage: www.sciencedirect.com/journal/biomarkers-in-neuropsychiatry

The potential of microRNAs as putative biomarkers in major depressive disorder and suicidal behavior

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ARTICLE INFO

Keywords:
Major depressive disorders
Suicidal behavior
microRNAs
Pathophysiology
Neuroplasticity

ABSTRACT

Major affective disorder are common and disabling conditions linked to significant psychosocial impairment as well as negative outcome (e.g., suicidal behaviors) . According to a molecular perspective, major depressive disorder and suicidal behavior have been associated with structural and synaptic plasticity disturbances. Small non-coding RNAs, such as microRNAs (miRNAs), may play a significant role in the translational regulation of the synapse. This comprehensive overview is aimed to carefully review the preclinical and clinical literature results regarding the involvement of miRNAs in the pathophysiology and pharmacotherapy of major psychiatric conditions . MiRNAs may act as gene expression regulators critically affecting brain development. The alteration of some intracellular mechanisms together with impaired assembly, localization, and translational regulation of specific RNA binding proteins may affect important functions such as learning and memory contributing to the pathophysiology of major depressive disorder and suicidal behavior. Based on the main findings, most of the miRNAs which have been identified to date are expressed in human brain, where they regulate prominent neurobiological processes, such as neurogenesis and neuroplasticity. The main implications of the present findings are critically discussed.

Introduction

Major affective disorders are relevant causes of morbidity worldwide and may be associated with negative outcomes such as suicidal behavior (Girardi et al., 2009; Pompili et al., 2013; Costanza et al., 2020a). Nearly 350 millions of individuals are affected by major depression and approximately 80,000 subjects die by suicide every year (for every completed suicide there are between 10 and 40 attempted suicides) (World Health Organization, 2012), but the pathophysiology of these conditions remain poorly understood (Costanza et al., 2020b). Thus, in order to clarify the most relevant molecular bases underlying major affective disorders and suicidality, the search of reliable biomarkers able to improve diagnosis, classifications and prognosis, but even produce endophenotypes, may guide tailored interventions for better outcomes.

During the past decades, one of the main focus of the research in this field was directed to the investigation of genes and heritability underlying these conditions, with the current perspective considering major affective disorders as the result of a complex combination between a genetic susceptibility and environmental factors (Gene X Environment) (Klengel and Binder, 2013). Several evidence supported the existence of a tight linkage between abnormalities in gene expression and the alteration of crucial neural circuits involved in affective regulation (Turecki, 2014; Autry and Monteggia, 2009) in key brain regions such as the prefrontal cortex (PFC) and hippocampus (Pittenger and Duman, 2008) with maladaptive changes in synaptic circuitry and connectivity as well as dendritic morphology (Gold et al., 2015). On the other side, environmental exposure to negative stressors in peri- and postnatal period are linked to severe somatic and mental diseases, such as major affective disorders, and suicidal behavior (Allen and Dwivedi, 2020). Recently, growing attention was moved to the biological interaction between genes and environment, increasingly highlighting the substantial role of epigenetics in mental disorders. The epigenetic regulation involves molecular systems able to adapt the expression of specific genes in relation to environmental demands (Escelsior et al., 2020). The

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https://doi.org/10.1016/j.bionps.2021.100035
Received 13 January 2021; Received in revised form 19 May 2021; Accepted 4 June 2021
Available online 19 June 2021

epigenetic controls on gene expression are exerted in particular through DNA methylation and histone modifications. More recently, an increasing number of results shed light on the relationship between epigenetic mechanisms and the activity of small non-coding RNAs. These RNAs, called microRNAs (miRNAs), are short molecules of about 22 nucleotides actively involved in post-transcription regulation of gene expression (Chuang and Jones, 2007). Notably, among the hundreds of those that were discovered to date, the most, different epigenetic perturbations may induce changes in genetic information processing pathways and are supposed to be correlated with the clinical presentations of affective episodes. Thus, the molecular mechanisms related to epigenetic regulation may be investigated in order to clarify the molecular biomarkers underlying affective disorders and suicidal behavior.

Overview of miRNAs: definition, diffusion and functions

MiRNAs were firstly discovered in 1993 as essential in the larval development of *Caenorhabditis elegans* (Lee et al., 1993). Later, they were characterized in both animal and vegetal reigns, showing a significant evolutionary stability (O'Connor et al., 2012) and confirming their importance in influencing biological processes.

MiRNAs comprise a large family of small noncoding RNAs that are typically ~22 nucleotides in length. Acting as key post-transcriptional regulators of gene expression (Huang et al., 2011), miRNAs are part of those molecular mechanisms known as epigenetic changes which are able to modify both cellular and subcellular functions (Yao et al., 2019).

As crucial modulators of more than 50% of gene-expression interactions by post-transcriptionally modifying the cellular stability of messenger RNA and thereby altering subsequent protein production, miRNAs may be related to various neurodevelopmental processes. MiRNAs are usually incorporated into the RNA-induced silencing (RISC) complex, which regulates gene expression by pairing primarily to the 3UTR region of protein coding mRNAs to repress target mRNA translation and/or induce target degradation (Filipowicz et al., 2008; Novina and Sharp, 2004). miRNAs have also the potential to increase translation of their mRNA targets, even though this is generally uncommon (Place et al., 2008).

Most of miRNAs are located in regions of genome distal to their targeted genes (Lagos-Quintana et al., 2001; Lau et al., 2001) whereas about 25% are located into the intronic regions of pre mRNAs (Bartel, 2004). As a single mRNA may be targeted by more than one miRNA, it may be inferred that miRNAs are sinchronely expressed. MiRNAs expression is usually extremely organized both temporally and spatially, as they are differently expressed in various neurodevelopment stages (Krichevsky et al., 2003; Lagos-Quintana et al., 2002; Podolska et al., 2011).

Various bioinoformatic tools have been designed to facilitate functional research into miRNAs and explore the specific role of miRNAs in both physiological and pathological processes. Importantly, miRBase (www.mirbase.org), the central depositary for miRNA data, acts as the arbiter of nomenclature for experimentally verified miRNAs. Through this website, primary and mature sequence and genomic data as well as data regarding the original discovery and publication of each experimentally verified miRNA may be easily accessed (Griffiths-Jones et al., 2006).

The involvement of miRNAs in neurobiological processes: understanding the possible sites of dysfunction

After transcription within the cell nucleus, primary miRNAs (pri-miRNAs) are cleaved by DROSHA (Drosha ribonuclease III) and DGCR8 (microprocessor complex subunit) into pre-miRNAs (precursor miRNAs). Then, pre-miRNAs are transported by esportin-5 in the cytoplasm and converted into a miRNA-miRNA duplex by the endoribonuclease (Dicer) and TRBP (TAR RNA-binding protein). This complex is bound by the Argonaut protein, which degrades one strand of the duplex, selecting the remaining one as the mature miRNA. The mature miRNA within the Argonaut Protein is known as RISC (RNA-induced silencing complex), as it is thought to repress the translation of mRNA into proteins (Kosik, 2006; Michalak, 2006) or degrading mRNA by slicing its sequence (Wahid et al., 2010). The nucleotide sequence of a mature miRNA is usually complementary to one or many mRNAs, usually binding the 3′ UTR of the targeted mRNA.

MiRNA biogenesis may be also regulated at the epigenetic level (Tardito et al., 2013a) as the methylation at the miRNA gene promoter may reduce transcription of pri-miRNAs by RNA Pol II, resulting in reduction of mature miRNAs and altered downstream repression of their targeted genes.

Long noncoding RNA (lncRNA) is another epigenetic modifier, the expression of which results altered in many pathological conditions such as repeated social defeat stress and major depression. A specific subtype of lncRNA, circRNA, may bind to mature miRNAs in the cytoplasm reducing miRNAs activity and indirectly increasing miRNA-target gene expression.

MiRNAs and pathologically stress-induced changes

Neuropsychiatric disorders are usually linked to the aberrant or inadequate response to stress. Cellular stress may induce significant alteration of homeostasis and damage of macromolecules such as protein deoxyribonucleic acid (DNA), RNA, and lipids. Growth arrest, repair, and clearance of damaged macromolecules and even programmed cell death (apoptosis) are all necessary to restorate the homeostasis and result in changes of the gene expression programs (Singh et al., 2019). Growing evidence reported the role of miRNAs as main regulator of cellular behavior, suggesting a significant role for these molecules in stress-induced conditions (Mendell and Olson, 2012). Stress may induce significant changes in miRNA biogenesis through methylation, histone modifications and other epigenetic mechanisms (Burns et al., 2018), with subsequent alteration of pathways and profile gene expression networks under their control (Olejniczak et al., 2018).

Both acute and chronic stress are demonstrated to alter miRNAs expression in the mammalian brain, inducing depressive and anxiety-like behaviors (Olejniczak et al., 2018). Furthermore, as some miRNAs are expressed at different neurodevelopmental stages (Dwivedi, 2014), they are of particular interest for understanding the impact of ELS during pre- and post-natal period on brain development and the subsequent vulnerability to neuropsychiatric disorders lifetime. Stress modulates several biological responses, culminating with HPA-axis (Whitnall, 1993) and immune system (Fagundes et al., 2013) activation resulting in alteration of the brain density matter (Ansell et al., 2012) and neuronal connectivity (Arnsten, 2015). Resilient individuals adapt to stress through a reversible dendritic remodeling in prefrontal cortex (PFC), amygdala, and hippocampus (McEwen et al., 2015). Conversely, non-resilient individuals are not able to reverse these changes, even after the removal of the stressing stimulus, and develop cumulative potentially persisting alterations in the brain functions (McEwen et al., 2016). Moreover, stress experienced during the prenatal period may determine an increased placental permeability to glucorticoids, indirectly affecting the fetal development and leading to a major susceptibility to depression in adulthood (Lyall et al., 2014; Czamara et al., 2019). Several studies in the last decade focused to clarify the epigenetic effects of postnatal stress on miRNAs expression and are reported afterwards.

MiRNAs alteration in neuropsychiatric disorders

MiRNAs may be investigated in specific neural cells but even in the whole blood, plasma, serum, cerebrospinal fluid (CSF), and saliva (Cortez et al., 2011; Cogswell et al., 2008; Mitchell et al., 2008; Mishra et al., 2016; Park et al., 2009). As miRNAs may result abnormally expressed in many tissues, the evaluation of their levels could provide

potentially useful biomarkers in specific neuropsychiatric conditions (Laterza et al., 2009; Skog et al., 2008; Beveridge et al., 2010). Particularly, as altered miRNAs levels have been observed in patients with schizophrenia and bipolar disorder (BD), as well as in depressed individuals who commit suicides (Kim et al., 2010; Moreau et al., 2011; Smalheiser et al., 2012a, 2014), they could be used as potential biomarkers for the diagnosis, management, treatment response, and neuroprogression of these conditions (Machado-Vieira et al., 2010; Saugstad, 2010; Dwivedi, 2011). For instance, mood stabilizers were reported to alter miRNAs levels in the rat hippocampus (Zhou et al., 2009) and lymphoblastoid cell lines of BD patients (Chen et al., 2009). A crucial role for miR-16 has been hypothesized concerning the mechanism of action of the antidepressant fluoxetine (Baudry et al., 2010), while desipramine was also reported to induce miRNAs modulation in rat hippocampus (Tardito et al., 2013b). In addition, ketamine (an NMDA receptor antagonist with antidepressant effect) and electroconvulsive shock therapy were found to reverse changes in miRNAs expression induced by early life stress in rat hippocampus (O'Connor et al., 2013a). Thus, a better understanding of miRNAs effects and their role in neuropsychiatric conditions might significantly help to clarify the complex mechanisms underlying the individual susceptibility to stress, reclassify groups of individuals into different diagnoses and endophenotypes, more accurately predict response or nonresponse to specific treatment options according to the new era of precision psychiatry (Tsankova et al., 2007).

Given this background, the present review aims to comprehensively analyze the current literature about the role of miRNAs as putative biomarkers in major affective disorders focusing on both preclinical and clinical evidence.

Methods

Data sources

A comprehensive search has been carried out on Medline and ScienceDirect databases up to May 2021. The following terms were used in the present search: ("Depression"[Mesh] OR "Depression"[all] OR "Depressive Disorder"[Mesh] OR "Depressive Disorder"[all] OR Suicide [Mesh) AND ("MicroRNAs"[Mesh] OR "MicroRNAs"[all]).

Eligibility criteria

We sought to include all studies reporting results published in peer-reviewed journals. Whether a specific title/abstract seemed to identify a study eligible for inclusion, the full-text article was examined in order to evaluate its relevance. Titles and abstracts were screened for inclusion by two researchers (A.T. and A.E.). We did not restrict the inclusion based on date of publication or study design but included only reports written in English. Possible discrepancies between the two reviewers who, blind to each other, explored the potential inclusion of the studies were resolved by consultations with a senior author (G.S.).

Results

Study selection

The search yielded a total of 5020 abstracts. After duplicates removal we screened by Title/Abstract 4934 records. Of these, the full text of 1124 articles was screened and yielded 48 studies eligible for inclusion, published between 1980 and 2021. The flowchart, with details on screening and reasons for exclusion, is reported in Fig. 1.

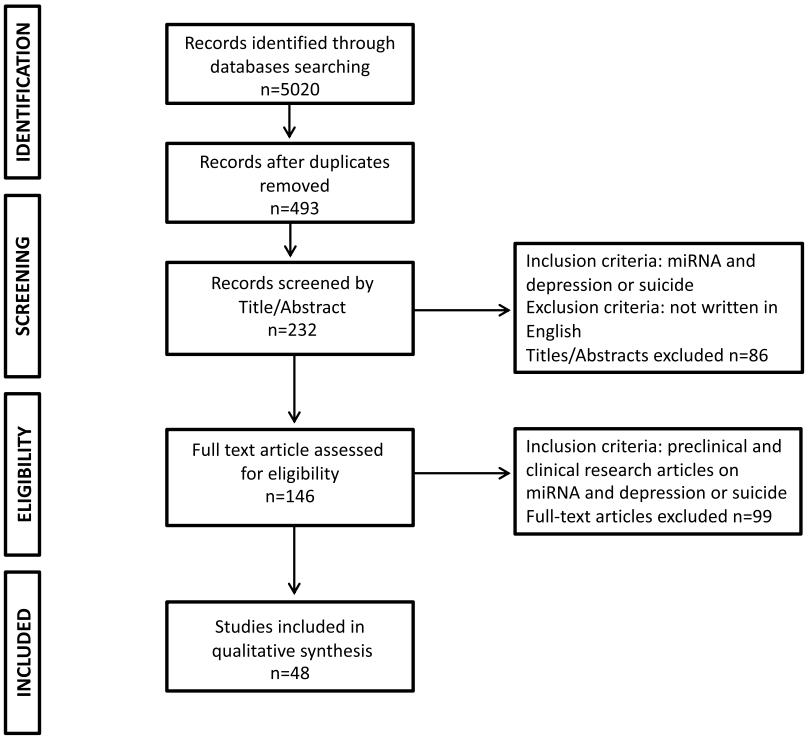

Fig. 1. The selected articles are categorized according to four different parts of the search process: identification, screening, eligibility and inclusion. The format of this figure is based on PRISMA 2009 guideline (Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097. doi: https://doi.org/10.1371/journal.pmed.1000097).

Study characteristics and main findings

MiRNAs alteration in animal models of major affective disorders

Table 1 reports study characteristics and main findings of the most relevant preclinical studies regarding the link between miRNAs, major affective disorders and suicidal behavior.

Most of existing preclinical studies have been conducted on rodents submitted to the following paradigms of stress (separated or combinated): maternal separation (MS) in the first 2–3 weeks of life; chronic unpredictable stress (CUPS) during childhood; acute stress (unescapable shock) during peri-pubertal period. These studies aimed to better understand the epigenetic role of stress in gene expression and brain development by targeting specific molecular pathways; differentiate resilient and non-resilient individuals (developing a depressed-like behavior) and identify specific subgroups of depressed patients based on antidepressant treatments in order to reverse epigenetic-induced dysregulations.

After acute stress, the expression of several miRNAs was increased in the frontal cortex, but not in the hippocampus of CD1 mice (Rinaldi et al., 2010). Increased expression of miR-134 and miR-183 was observed in the amygdala following acute stress, when compared to unstressed controls. Chronic stress decreased miR-134 levels, whereas miR-183 remained unchanged in both the amygdala and hippocampus. Importantly, miR-134 and miR-183 share a common predicted mRNA target, encoding the splicing factor SC35. Stress was previously shown to upregulate SC35, which promotes the alternative splicing of acetylcholinesterase (AChE) from the synapse-associated isoform AChE-S to the soluble AChE-R protein. Knockdown of miR-183 expression increased SC35 protein levels in vitro, whereas overexpression of miR-183 reduced SC35 protein levels, suggesting a specific role of miR-183 in stress regulation. Stress-induced changes in miR-183 and miR-134 modify both alternative splicing and cholinergic neurotransmission in the stressed brains (Meerson et al., 2010). Uchida et al. (2010) reported that 3 h of daily maternal separation in 14 days old rats resulted in upregulation of miR-132, miR-124, miR-9 and miR-29a in PFC as well as depressive and freezing behavior as social defeat stress response (Chen et al., 2015). MiR-124 is implicated in neuronal differentiation by regulating brain-derived neurotrophic factor (BDNF) (Sonntag et al., 2012) while miR-132 plays an important role in morphogenesis (Wanet et al., 2012). Both of these miRNAs remained upregulated at post-natal day (PND) 60, suggesting a stable change induced by ELS. Huang et al. (Huang and Li, 2009) found the up-regulation of miR-504 in the Nucleus Accumbens (NA) after 6 h of daily MS in PND 1-14. In addition, miR-504 targets the 3′UTR region of dopamine receptor 1(DRD1) gene, implicated in the development of anhedonic behavior in rodents. Bahi et al. (Bahi, 2016) investigated the impact of lentiviral-mediated overexpression of miR124a into the dentate gyrus (DG) on social interaction, repetitive- and anxiety-like behaviors in the neonatal isolation (Iso) model of autism. Rats isolated from the dams on PND 1 to PND 11 displayed decreased social interaction contacts and increased repetitive- and anxiety-like behaviors. This study attributes neonatal isolation-inducible cognitive impairments to induction of miR124a and consequently suppressed BDNF mRNA. Other studies compared ELS inducted by maternal deprivation (MD) to CUPS. Bai et al. (2012) reported that MD and CUPS induced different depression-like behaviors in rats. Depression induced by MD but not by CUPS was significantly associated with upregulation of miR-16 and possibly subsequent downregulation of BDNF in the hippocampus. Zhang et al. (2015) found that ELS enhanced the susceptibility to late life stress and resistance to escitalopram treatment through decreasing miRNA-9 expression and subsequently upregulating DRD2 expression in the NA. MiRNA-326 may be a novel target of escitalopram. O'Connor et al. (2013b) investigated the differential response to fluoxetine (flu), ketamine (Ket) and electroconvulsive therapy (ECT) in rodent pups exposed to 3 h of daily MS and found that antidepressant treatments reversed some of these effects including a stress-induced change to miR-451. Ketamine and ECT had the highest number of common targets suggesting convergence on common pathways. Interestingly all three treatments possessed miR-598-5p as a common target. Other studies on animal models were conducted in the peri-pubertal period (from PND-28). For instance, Xu et al. (2017) focused on HPA-axis activation role in the determination of depressive-like behaviours in adolescent and adult rats. CUMS and dexamethasone administration by PND 55 induced permanent anhedonic behaviours, memory impairment and glucorticoid receptor (GR) decreased expression, through the up-regulation in the basolateral amygdala (BLA) of miR-124a and miR-18a. These miRNAs are involved in the regulation of FK506 binding protein51 (FKBP5), the co-chaperone protein of GR. Adolescent and adult rats were exposed to inescapable stress during their adolescence by Liu et al. (2017). Early adolescent stress induced anxiety-like behaviors and spatial memory damage: decreased miR-135 expression was associated with increased the serotonin 1a receptor (5-HT1AR) expression in PFC and increased miR-16 expression in the hippocampus (HIP) of exposed rats. Paroxetine hydrochloride and corticotropin-releasing factor antagonist (CP-154,526) reduced depressive symptoms and neutralized the dysregulation of miRNA-135a, miRNA-16, and 5-HT1AR expression in stressed rats. Conversely, Vogel et al. (Vogel Ciernia et al., 2018) explored the epigenetic effect of augmented maternal care (AMC), obtained through the brief removal of the pups from the dam. AMC, consisting of increased liking, grooming, and nursing of the pups, has a positive impact on brain development due to the reprogramming of neonatal HPA circuits (Korosi and Baram, 2009) and increased resilience to stress and enhanced learning and memory (Viau et al., 1993; Plotsky and Meaney, 1993; Meaney and Aitken, 1985). AMC increases expression of miR-488, mi-144, and mi-542-5p and decreases the expression of miR-421 and mi-376b-5p. These miRNAs target a number of genes relevant to stress signaling pathways and neuronal regulation, such as Crh and Nr3c1. A comparison between acute- and chronic-stress-related changes in miRNA profiles expression was carried out by Aten et al. (2019). After 5 -hs acute stress, miR-132 and miR-212, involved in the development of anxiety-related behaviors, were increased more than two-fold in the WT murine Hip and amygdala, while the expression of both miR-132 and miR-212 was upregulated more than two-fold within the amygdala but not in the Hip after a 15 day chronic-stress paradigm. Based on emerging evidences, miR-138 and SIRT1 play a crucial role in MDD. Li et al. (2020) analyzed by RT-PCR or Western blotting the expression level of miR-138 and SIRT1 in CUMS model, inducing depressive-like behaviors through forced swimming test (FST) and sucrose preference test (SPT). miR-138 was found unregulated in the hippocampus of the CUMS mice and correlated with decreased SIRT1 expression.

Roy et al. (2020) inducted learned helplessness (LH) behavior in PND 90 rats by giving inescapable tail shocks followed by escape tests. Amygdala-specific altered miRNAs were determined following next-generation sequencing method and findings from the rat in vivo model were replicated in postmortem amygdala of MDD subjects. miR-128-3p was found upregulated in LH rats. The increase in expression of amygdalar miR-128-3p along with significant downregulation of key target genes from Wnt signaling (WNT5B, DVL, and LEF1) was found in MDD subjects. According to evidences, miR-15b is up-regulated in MDD subjects. Guo et al. (2020) determined the expression level of miR-15b in the Nucles Accumbens (NA) of CUMS rats and compared with a control group. The application of a miR-15b antagomir into the nucleus accumbens reduced the incidence of CUMS-induced depression and reversed the attenuations of excitatory synapse and syntaxin-binding protein 3 (STXBP3A) /vesicle-associated protein 1 (VAMP1) expression. The treatment of anti-microRNA-15b-5p may convert stress-induced depression into resilience. Sun et al. (2021) induced a depression-like behavior and memory disorder in mouse model by means of intraperitoneal injection with lipopolisaccaride (LPS) in order to analyze miR-96 level expression in the HC. The expression of miR-96 was increased, whereas that of SV2C was decreased in the CA1

Table 1
Preclinical studies regarding the alteration of miRNAS in animal models of major affective disorders.

Authors	Study technique	Involved miRNA	Targeted proteins and genes	Source	Comments
Uchida et al. (2010)	3 h daily maternal separation	↑ MiR-124; ↑ miR-132; ↑ miR-9; ↑ miR-29a	Mcl-1; REST4; HECTD1	PFC	MiR-124 and miR-132 resulted crucial for brain development as they were involved in neuronal differentiation (miR-124) and morphogenesis (miR-132). MiR-9 regulates microglia function through its target HECTD1 and miR-29a has been implicated in apoptotic pathways by targeting Mcl-1.
Rinaldi et al. (2010)	Restraint stress (2 h for 1 or 5 days)	↑ Let-7a; ↑ miR-9; ↑ miR-26a/b	HECTD1	PFC	The increase in the expression of different miRNAs was prominent after acute stress while only minor changes were observed after repeated restraint.
Meerson et al. (2010)	Comparison between acute and chronic stress (chronic immobilization)	MiR-134; miR- 183	SC35 involved in the alternative splicing of AChe of the synapse-associated isoform AChE-S	Amygdala and hippocampus	Both miR-134 and miR- 183 levels were increased after acute stress while miR-134 levels were reduced by chronic stress in the amygdala. Stress-induced changes in miR-183 and miR-134 modified both alternative splicing and cholinergic neurotransmission in the stressed brains.
Bai et al. (2012)	6 h of daily MD compared with CUPS	↑ miR-16	↓ BDNF	Hippocampus	MD and CUPS induced different depression-like behaviors in rats. Depression induced by MD but not CUPS was significantly associated with upregulation of miR-16 and possibly subsequent downregulation of BDNF in the hippocampus.
O'Connor et al. (2013)	Effect of 3 h of MS, AD treatment (Flu, Ket) and ECT on hippocampal miRNAs measured by quantitative real-time PCR	↓ MiR-598-5p; ↓ miR-451	CREB5; $GABA_A$-R associated protein; muscarinic cholinergic receptor 5	Hippocampus	Flu modified the levels of MiR-598-5p and miR-451; Ket ten miRNAs concentrations and ECT 14 miRNAs levels. ECT and Ket shared three miRNA targets while Flu, Ket and ECT treatments significantly increased the levels of hippocampal miR-598-5p. MS significantly reduced miR-451 levels while this effect was reversed by Flu treatment.
Zhang et al. (2013)	6 h of daily MS from PND 1–14	↑ MiR-504	3'UTR DRD1	NA	DRD1-containing neurons have been shown to play an important role in the development of anhedonic behavior in rodents
Zhang et al. (2015)	6 h of daily MD compared with CUPS	↓ MiR-9; ↑ miR-326 in the NA; ↓ levels in the striatum	HECTD1 ↑ 3'UTR DRD2	NA and striatum	CUPS alone is able to induce depression-like behaviors in rats, MD enhances the effect of CUPS on DRD2 gene and miR9 expression (decreased in NA by CUPS and striatum by MD). Both CUPS and MD have an effect on miR-326 expression (increased in NA and decreased in the striatum by CUPS; elevated by MD in the striatum). Escitalopram normalized miR-326 expression but had no effect on the expression of miRNA-9, DRD2 mRNA, and DRD2 protein in both NA and striatum. Only miRNA-9 directly targets the 3'UTR of DRD2 mRNA and inhibits DRD2 protein expression. Overall, escitalopram significantly decreased depression-like behaviors in CUPS rats but was less effective in MD with CUPS rats.
Bahi et al. (2016)	Half of a litter separated from dam, while other half remained with dam	↑ miR-124	↓ BDNF	DG	Stereotaxic injection of a miR-124 lentivirus into the hippocampus induced the down-regulation of BDNF expression only in maternally separated pups.
Xu et al. (2017)	CVS by PND 55	↑ MiR-124; ↑ miR-18a	FKBP5/GR; BDNF	BLA	CVS and dexamethasone administration by PND 55 induces depressive-like behaviours by permanent up regulation of miR-124a and transient upregulation of miR-18a in BLA and subsequent decrease of GR levels. Injection of RU486, a CR antagonist, reverses both the effects of CUPS and dexamethasone administration on miRNAs expression.
Liu et al. (2017)	Inescapable shock to chronically stressed adolescent rats	↓ MiR-135a; ↑ miR-16	5-HT1AR	PFC (miR-135a) hippocampus (miR-16)	A reduction in miRNA-135a expression was associated with increased 5-HT1AR expression in PFC and increased miRNA-16 expression in the HIP of stressed rats. Drug treatments alleviated behaviors and reversed the miRNA-135a, miRNA-16, and 5-HT1AR expression in stressed rats.
Vogel Ciernia et al. (2018)	MS in short bouts of 15 min to induce AMC	↑ MiR-488; ↑ miR−144; ↑ miR−542-5p; ↓ miR-421; ↓ miR-376b-5p	Crh; Nr3c1	Hypotalamus; PFC	MiR-144 is predicted to target galanin, a protein important to the noradrenergic system and responsive to restraint stress in rodents. In panic and anxiety disorder, miR-488 has been shown to regulate proopiomelanocortin, a precursor to adrenocorti- cotropin. Another predicted target of miR-488, arginine vasopressin receptor 1a was recently shown to be downregulated in mice after ELS.
Aten et al. (2019)	5-h acute-stress model compared with 15 days chronic stress paradygm	↑ MiR-132; ↑ miR-212	Sirt-1; Pten	Amygdala Hippocampus	MiR-132 and miR-212 increased more than two-fold in the WT murine hippocampus and amygdala after

(*continued on next page*)

Table 1 (*continued*)

Authors	Study technique	Involved miRNA	Targeted proteins and genes	Source	Comments
					acute stress; miR-132 and miR-212 upregulated more than two-fold within the amygdala but not in the hippocampus after chronic stress. Suppression of transgenic miR-132 expression (via doxycycline administration) mitigated the anxiety-related behaviors.
Roy et al. (2020)	All animal-related experiments were performed in postnatal day-90 male Holtzman rats. LH behavior was inducted by giving inescapable tail shocks on days 1 and 7 followed by escape tests on days 2, 8, and 14	↑miR-128-3p	Dlv1; Lef1	Amygdala	miR-128-3p is one of the most significantly upregulated miRNAs in susceptible (LH) rats, appeared to be closely associated with Wnt signaling disruption by targeting select Wnt ligands (Wnt3/5), intracellular signal transducer (Dvl1), and pathway specific downstream transcription factor (Lef1). In addition, our study showed a mechanistic association between transcription repressor Snai1 and miR-128-3p, where reduced expression of Snai1 might cause induced expression of miR-128-3p in LH rats.
Li et al. (2020)	The expression level of miR-138 and SIRT1 were analyzed by RT-PCR or Western blotting in CUPS) model. The depressive-like behaviors were analyzed by FST and SPT in mice injected with miR-138 and SIRT1 overexpression lentivirus.	↑miR-138	Sirt-1	Hippocampus	The upregulation of miR-138 was found in the hippocampus of the CUMS mice and correlated with decreased SIRT1 expression. C57BL/6 J mice treated with SIRT1- and miR-138-expressing (miR-138) lentivirus showed increased depressive-like behaviors.
Guo et al. (2020)	A group of CUPS mice was compared with a control group for an observational time of 3 weeks. Mood state was assessed by SPT, YMT and FST.	↑miR-15b	STXBP3A VAMP1	NA	The application of a microRNA-15b antagomir into the nucleus accumbens significantly reduced the incidence of CUMS-induced depression and reversed the attenuations of excitatory synapse and syntaxin-binding protein 3 (STXBP3A) /vesicle-associated protein 1 (VAMP1) expression. The treatment of anti-microRNA-15b-5p may convert stress-induced depression into resilience.
Sun et al. (2020)	A depression-like behavior and memory disorder mouse model was established by means of intraperitoneal injection with LPS.	↑miR-96	SV2C	Hippocampus	miR-96 negatively regulates the expression of SV2C, which is expressed in a variety of cell types, particularly dopaminergic, GABAergic, and cholinergic cells. The deletion of SV2C has been reported to trigger a decrease in striatal dopamine release, contributing to the genesis of depressive-like behavior.
Yang et al. (2021)	A group of male mice was exposed to CUMS and then mood-state was assessed by FST and SPT.	↑miR-17-5p ↑miR-7b-5p	Wfs1	Hippocampus	Wfs1, one of the top ten DEGs, was identified as the key regulator of the cell cycle and the participator in the highest number of modules screened out in PPI networks. In this study the downregulation of Wfs1 and upregulation of UBTF/mmu-mir-17-5p/mmu-mir-7b-5p in the hippocampus of the CUMS mouse model was confirmed. Wfs1 and related molecules were predicted to be associated with the pathological process of depression.

Note: Acetylcholine (AChe); Acetylcholinesterase (AChE-S); Antidepressant (AD); Augmented Maternal Care (AMC); Basolateral Amygdala (BLA); Brain Derived Neurotropic Factor (BDNF); Corticosteroid Receptor (CR); Chronic Variable Stress (CVS); Chronic Unpredictable Stress (CUPS); Corticotropin Releasing Hormon (Crh); daily maternal separation (MS); Dentate Gyrus (DG); dopamin receptor 2 (DRD2); Electroconvulsive shock therapy (ECT); Early Life Stress (ELS); Fluoxetine (flu); FK506 Binding Protein (FKBP5); Force Swimming Test (FST); Glucorticoid Receptor (GR); learned helplessness (LH); Lipopolisaccaride (LPS); Nucleus Accumbens (NA); Prefrontal cortex (PFC); Induced myeloid leukemia cell differentiation protein (Mcl-1); E3 ubiquitin-protein ligase (HECTD1); maternal deprivation (MD); Nuclear Receptor Subfamily 3 group C Member 1 (Nr3c1); Polymerase Chain Reaction (PCR); Post Natal Day (PND); $GABA_A$ receptor ($GABA_A$-R); Phosphatase and tensin homolog (Pten); RE-1 Silencing Transcription Facor-4 (REST4); Serin/arginine-rich splicing factor (SC35); Sirtuin-1 (Sirt-1); Sucrose Preference Test (SPT); 3' Untranslated Region (3'UTR); DRD1 (dopamin receptor 1); Wild Type (WT); Serotonin 1A Receptor (5-HT1AR); Y-maze Test (YMT).

region of mice exhibiting depression-like behavior and memory impairment. Yang et al. (2021) investigate the differentially expressed genes (DEG) in the hippocampus in CUMS rats. Wfs1 was down regulated and UBTF/mmu-mir-17-5p/mmu-mir-7b-5p up regulated in the hippocampus of the CUMS mouse model, indicating how Wfs1 and related molecules could be associated with the pathological process of depression.

MiRNAs and stress regulation: preclinical and clinical evidence. The most relevant preclinical/clinical evidence investigating the link between pathologically stress-induced changes and miRNAs are briefly summarized in Table 2.

MiRNAs and major affective disorders: clinical evidence. Table 3 summarized the most relevant clinical studies regarding the link between miRNAs changes and major affective disorders.

In a case-control study, Suderman et al. (2014) compared whole blood sample of 12 males with a positive history of childhood abuse and maltreatment with 28 without such a history. Interestingly, abuse-associated methylation was observed in 39 miRNAs and in 6 miRNAs the hypermethylated state was consistent with the hypomethylation of their downstream gene targets.

In another case-control study, Prados et al. (2015) found lower methylation level of the promoter region of miR-124-3 in the circulating leucocytes in 96 Borderline Personality Disorder (BPD) patients

Table 2
MiRNAs and stress regulation: preclinical and clinical evidence.

MiRNA	Target	Main findings
↑ MiR-124	BDNF ↓	MiR-124 was increased after MS and corticosteroid injection in rats; miR-124 was also increased in blood of MDD and BPD patients with a positive history of traumatic experiences. ELS sensitizes GC pathways causing depression- or anxiety-related behavioral outcomes either in animals and humans.
↑ MiR-16	5 H T neurotransmission system	miR-16 upregulated in the hippocampus of rats after MS, inescapable shock, CUPS. miR-16 upregulated in blood of SZ patients with child abuse history.
MiR-18a; miR-9; miR-29; miR-200; miR-125	FKBP5; HECTD1; Mcl-1; CYP11B2	These miRNAs are upregulated in the hippocampus after both maternal separation and inescapable shock in rodents as well as in blood from healthy individuals with ELS history.

Note: Borderline Persnality Disorder (BPD); Cytochrome P45011B2 (CYP11B2); Chronic Unpredictable Stress (CUPS); Early Life Stress (ELS); FKBP Prolyl Isomerase 5 (FKBP5); Guanyl-Cyclase (GC); HECT Domain E3 Ubiquitin Protein Ligase 1 (HECTD1); Major Depressive Disorder (MDD); Induced myeloid leukemia cell differentiation protein (Mcl-1); Maternal separation (MS); Schizophrenia (SZ).

compared with MDD subjects. MiR-124 may be considered the more represented miRNA in neurons and it is implicated in neurogenesis and neural differentiation.

A study on 32 patients conducted by Cattane et al. (2019) investigated the role of ELS in late-onset schizophrenia. Interspecific studies found miR-125-1-3p decreased in both prenatal stressed rodents and whole blood of schizophrenic patients. Hip miR-125-1-3p is implicated in the corticosteroid signaling relevant to stress due to its response to cortisol treatment. Indeed, miR-125-1-3p has been shown to target aldosterone synthase (CYP11B2) (Robertson et al., 2017), the final enzyme in the conversion of cholesterol into the mineralocorticoid, aldosterone (Connell and Davies, 2005).

MiRNAs and suicidal behavior: clinical evidence

Table 4 summarized the clinical studies regarding the link between miRNAs changes and clinical evidence regarding suicidal behaviour.

The stress–diathesis model assumes that suicide is the result of the interaction between state-dependent (environmental) stressors and a trait-like diathesis or susceptibility to suicidal behaviour, independent of psychiatric disorders. Early-life adversity and epigenetic mechanisms seem to be related to causal mechanisms for this diathesis (Mann and Haghighi, 2010). Findings from cross-sectional and longitudinal studies showed that early-life adverse events, particularly multiple abuse/maltreatment, are one of the strongest risk factors for suicide, even after adjustment for psychopathology (Brodsky et al., 2008). Epigenetic mechanisms might explain the association between childhood experiences and abnormal reactivity to stressors in later life, at least partially mediated by HPA-axis impairment (Turecki et al., 2012a). Both post-mortem and in-vivo studies indicate the role of serotoninergic and noradrenergic transmission as well as for the HPA axis in the diathesis for suicidal behaviour (Mann and Currier, 2010). Serotoninergic transmission is impaired in cortical and subcortical regions of patients died by suicide (Bondy et al., 2006). Similarly, a reduction of serotoninergic neurons in the raphe troncoencephalic nucleus was reported (Drevets et al., 2007), with a compensatory up-regulation of post-synaptic 5 H T1A and 5 H T2A receptors in the ventral prefrontal cortex (Stanley and Mann, 1983). Impairment of serotoninergic transmission has been associated with the increased impulsivity, typical of individuals committing suicide (Glick, 2015). Other evidence show a deficiency of noradrenergic neurons in the locus coeruleus (LC) of subjects died by suicide, and lower 3-methoxy-4-hydroxy-phenylglycol (MHPG) concentrations in the CSF seem to predict the risk to attempt suicide in individuals with MDD (Arango et al., 1996).Although the importance of HPA abnormalities in suicidal behavior is well known, a better comprehension about the mechanisms involved in these dysfunctions is needed. MD in infant rats causes DNA methylation of the GR, resulting in less expression, impaired feedback inhibition, and excessive release of cortisol after adult stress (Liu et al., 1997; Ladd et al., 2005). Suicide completers with a previous history of childhood adversities (CA) showed an increased methylation of GR promoter and a reduced expression of GR gene in the Hip. This methylation pattern was not shared by suicidal individuals who did not report CA supporting the hypothesis that the resistance to dexamethasone is a risk factor for suicide (Turecki et al., 2012b). Furthermore, excess of plasma cortisol resulted to be neurotoxic as it diminishes 5-HT1A receptor expression in the Hip (Chalmers et al., 1993; McEwen, 2005). Abnormalities in multiple genes correlated with glial cells, glutamate and γ-aminobutyric acid (GABA) cortical neurotransmitters, growth factors, polyamides and synaptic vesicles were found and presumably repleted in miRNAs changes in suicide completers with and without affective disorders (Fiori and Turecki, 2012). Suicide completers showed an abnormally reduced expression of GABA neurons in the Hip and other cortical regions (Bielau et al., 2007). The role of glutamate in suicide is far from being completely understood, nevertheless the neurotoxic action of this neurotransmitter might

Table 3
Most relevant clinical studies about miRNAs and major affective disorders.

Author(s)	Study design	Sample	Cell type	miRNAs involved	Targeted genes	Main conclusions
Suderman et al. (2014)	Case-control study	n = 40 males, of which 12 with child abuse history and 28 without	Whole blood	Methylation of promoter region of miR-514, miR-520c, miR-215, miR-519a, miR-519e, miR-203, miR-let7d	PM20D1; SLC17A3	Genome-wide methylation profiles in adult DNA were associated with childhood abuse.
Prados et al. (2015)	Case-control study	n = 189, of which 96 patients diagnosed with BPD and 93 diagnosed with MDD	Blood leucocytes	Methylation of the promoter region of miR-124-3	NR3C1 (GR gene); EFNB1	MiR-124-3p associated with severity of childhood trauma as well as BPD symptom severity.
Cattane et al. (2019)	Case-control study	n = 33, of which 11 patients with trauma history and 22 patients without trauma history	Whole blood	↑ MiR-29b-3p; ↑ miR-29c-3p; ↑ miR-16-5p; ↓ miR-200b-5p; ↓ miR-125b-1-3p	CYP11B2	Decreased miR-125-1-3p in whole human blood and hippocampus of prenatally stressed rodents. MiR-125-1-3p specifically related to ELS, as it targets CYP11B2, the final enzyme in the conversion of cholesterol into aldosterone.

Note: Borderline Personality Disorder (BPD); aldosterone synthase (CYP11B2); Ephrin B1 (EFNB1); Desossiribonucleic Acid (DNA); Early Life Stress (ELS); Major Depression Disorder (MDD); Nuclear Receptor Subfamily 3 group C Member 1 (NR3C1); Peptidase 20 Domain 1 (PM20D1); Sodium-dependent Phosphate Transport Protein 4 (SLC17A3).

Table 4
Post-mortem studies concerning the link between miRNAs and suicidal behavior.

Authors	miRNA	Regulation	Locus	Main findings
Smalheiser et al. (2012)	MiR-142-5p, miR-33a, 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-552, miR-453, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p	Downregulated	PFC	MiRNAs targeting DNMT3B, BCL2, VEGFA, NOVA1 genes were involved in cellular growth, differentiation, signaling and plasticity.
Ernst et al. (2009, 2011); Maussion et al. (2012)	MiR-185	Downregulated	PFC	MiR-185 was negatively correlated with Trkb-T1 expression in the PFC.
Lopez et al. (2014)	MiR-1202	Downregulated	PFC	MiR-1202 was negatively correlated with GRM4 expression, a receptor protein implicated in glutamatergic, dopaminergic, gabaergic and serotonergic neurotransmission.
Lopez et al. (2014)	MiR-139-5p; miR-320c; MiR34c-5p	Upregulated	PFC	MiR-139-5p and miR-320c were inversely correlated with polyamine gene SAT1 while miR34c-5p and miR-320c were inversely correlated with polyamine gene SMOX
Maheu et al. (2015)	MiR-511	Upregulated	Basolateral amygdala	MiR-51 targeting GDNF receptor GFRα1a was involved in signaling cascade of glial population cells in depressed brains.
Aschrafi et al. (2016)	MiR-326	Upregulated	Rostroventral midbrain area within the centrally projecting EWcp	Ucn1 gene expression was involved in coping response to stress.
Torres-Berrío et al. (2017)	MiR-218	Downregulated	PFC	Increased expression of DCC was able to induce increased vulnerability to stress.
Roy et al. (2017)	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; MiR-409-5p, let-7g-3p, miR-1197	Upregulated Downregulated	LC	The development of a miRNA network was specific to suicide and absent in the control group.
Wang et al. (2018)	MiR-19a-3p	Upregulated	PFC	MiR-19a-3p increased TNF-α expression.
Squassina et al. (2020)	MiR-4286	Downregulated	PFC	MiR-4286 targeting 17 genes was involved in lipid and glucose metabolism which were partially dysregulated in postmortem brains from BD suicide patients.

Note: B-cell lymphoma 2 (BCL2); Bipolar Disease (BD); Edinger–Westphal nucleus (EWcp); Deleted Colorectal Cancer (DCC); DNA (cytosine-5-)-methyltransferase 3 beta (DNMT3B); Glial cell-derived neurotrophic factor (GDNF); Glial cell-derived neurotrophic factor family receptor alpha-1 (GFRα1a); Glutamate Metabotropic Receptor 4 (GRM4); Locus Coeruleus (LC); microRNAs (miRNAs); negative influence on urocortin 1 (Ucn1); NOVA Alternative Splicing Regulator 1 (NOVA1); prefrontal cortex (PFC); Spermidine/Spermine N1-Acetyltransferase 1 (SAT1); Spermine Oxidase (SMOX); Truncated isoform of tyrosine receptor kinase B (Trkb-T1); Vascular endothelial growth factor A (VEGFA).

enhance the cortisol toxicity, contributing to deficits in neurons reported in depressed subjects who died by suicide (McEwen, 2012). Among neurotrophic factors, a significant depletion of BDNF and its receptor TrkB has been found both in the whole blood and brain of depressed individuals died by suicide (Hashimoto, 2010), and variation in BDNF plasma levels has found to be associated to response to antidepressants (Fornaro et al., 2015) Finally a possible role for polyamine-mediated apoptosis in susceptibility to suicidal behaviour via a neurodegenerative reduction of grey-matter volumes has been proposed (Le-Niculescu et al., 2013). A downregulation of SAT-1, gene encoding for the enzyme involved in polyamine catabolism, emerged in the amygdala, Hip, and cingulate cortex of suicidal individuals (Sequeira et al., 2007; Guipponi et al., 2009; Klempan et al., 2009). According to the preclinical and clinical evidence exposed afterwards, miRNAs, as mega controllers of gene regulatory events, may exert a crucial role in the epigenetic regulation of complex phenomena such as suicidal behaviour but, interestingly, they might also represent the target for tailored interventions in subjects at risk for suicide.

MiRNAs and suicidal behavior: post-mortem studies

Table 4 summarized the most relevant clinical studies regarding the link between miRNAs changes and clinical evidence regarding the post-mortem findings on subjects who committed suicide.

Changes in miRNAS expression in the dorsolateral prefrontal cortex (dlPFC) of depressed subjects were found by Smalheiser et al. (2012b). In particular, miRNAs were measured in PFC of 18 AD-free depressed suicide committers and 17 non-psychiatric controls and miRNA expression was found globally down-regulated in PFC of depressed suicide subjects. A set of 29 miRNAs was found largely associated in the suicidal depressed brain: these miRNAs were found to target several genes (e.g., DNMT3B, BCL2, VEGFA, NOVA1), involved in cellular growth, differentiation, signaling and plasticity. Moreover, Maussion et al. (Ernst et al., 2009) reported a role for miR-185 in the regulation of BDNF receptor, TrkB-T1, the downregulation of which has been associated with suicidal behavior. In fact, BDNF is a critical growth factor involved in the maturation of neurons, including neuronal morphology and synapse refinement (Ernst et al., 2011; Holt et al., 2019). Lopez et al. (2014a) found that the down-regulated expression of miR-1202 in the PFC of depressed suicide subjects was negatively correlated with the expression of the metabotropic glutamate receptor (GRM4), a receptor protein of glutamatergic, dopaminergic, GABAergic and serotonergic neurotransmission. Furthermore, the same researchers focused on the regulatory role of miRNAs in polyamine genes expression in suicidal subjects (Lopez et al., 2014b). Both preclinical (Uchida et al., 2011) and clinical studies (Ma et al., 2013a; Wang et al., 2014) supported the role of glial cell line- derived neurotrophic factor (GDNF) in determining neuroplastic remodeling and clinical response to AD treatments. Maheu et al. (2015) found an isoform-specific decrease in GDNF family receptor alpha 1 (GFRA1) mRNA expression, resulting in lowered GFRα1a protein levels in basolateral amygdala (BLA) samples from suicidal subjects. The downregulation of GFRα1a was associated with increased expression of miR-511, predicted to target the 3′-UTR-containing transcripts (GFRA1-L) coding for GFRα1a.

Urocortin-1 (Ucn-1) is a stress-mediated neuropeptide acting upon

central stress regulatory pathways in response to acute stress. MiR-326 regulates Ucn1 mRNA and protein expression in neurons. Aschrafi et al. (2016) found abnormally reduced levels of miR-326 in both rats with stress-induced depressed-like behavior and suicide attempters and completers together with increased levels of Ucn-1 in the rostroventral midbrain area within the Edinger–Westphal nucleus (EWcp). Netrin-1 guidance cue receptor gene, deleted in colorectal cancer (DCC), showed a significative action in axon arborization, dendritic growth, and synapse formation; its mRNA expression is regulated by miR-218. Torres-Berrio et al. (Torres-Berrío et al., 2017) found reduced miR-218 levels in PFC of depressed suicidal subjects suggesting that the absence of its antagonizing function on DCC expression may lead to synaptic remodeling in the pyramidal neurons of MDD brains. Moreover, Roy et al. (2017a) found dysregulated patterns of miRNAs expression in the locus coeruleus (LC) of depressed suicide committers. Furthermore, the role of neuroinflammation in the pathophysiology of suicidal behavior has been intensively investigated in the last decade, with a particular focus on proinflammatory cytokines. To this regard, Wang et al. (2018a) found upregulated miR-19a-3p associated with increased levels of tumor-necrosis-factor α (TNF-α) in the dlPFC of both suicide completers and MDD patients died for other causes than suicide. Recently, Squassina et al. (2020) measured miRNAs expression in lymphoblastoid cell lines (LCLs) from suicidal BD patients and a healthy control group, finding increased miR-4286 and decreased miR-186-5p in the BD group. Pathways analysis on predicted-miR-4286 targets include 17 genes, involved in lipid and glucose metabolism. Finally, BD patients treated with lithium showed reduced expression of miR-4286 compared to non-treated patients.

miRNAS, major affective disorders, and suicide: the promise of a better future. According to the differential miRNAs levels in peripheral fluids, such as plasma, serum or saliva, detecting changes in their profile expression might be useful to mark various neuropsychiatric diseses (Rao et al., 2013; Chen et al., 2008; Dorval et al., 2013; Fichtlscherer et al., 2010; Jin et al., 2013; Ma et al., 2013b; Gaughwin et al., 2011; Liu et al., 2010; Kalani et al., 2014; Keller et al., 2011). Identifying the levels of specific miRNAs may be of particular interest given that actively secreted miRNAs are protected from degradation (Alvarez-Erviti et al., 2011) as they are wrapped in exosomes (Lakhal and Wood, 2011; Valadi et al., 2007; Vickers et al., 2011) and may easily pass the blood-brain barrier. Furthermore, psychoactive medications are able to reverse/attenuate miRNA dysregulations in blood sample, suggesting that miRNAs might be use to predict response or nonresponse to treatments (Murakami et al., 2010; Gámez-Pozo et al., 2012). Emerging evidence are also showing how MDD is not may be considered the phenotypical expression of an inflammatory disorder (Raison and Miller, 2011). Thus, measuring miRNAs profile expression in specific immune cells such as white blood cells (WBC) could provide useful markers for MDD. Unfortunately, there are still several limitations related to the use of miRNAs as diagnostic and prognostic biomarkers, due to their heterogeneous distribution (Dwivedi, 2018). Belzeaux et al. (2012) firstly divided MDD responder and non-responder to AD treatment, according to their different peripheral transcriptional signatures during mood episodes. They reported that eight miRNAs showed significant variation in expression among patients with clinical improvement but only miR-941 and miR-589 remained stably overexpressed during the 8-weeks-follow-up. Fourteen dysregulated miRNAs had mRNA targets assumed to be differentially expressed in MDD patients: (a core of four genes involved in the catabolism of lipid-modified proteins, chromatin organization and pro-inflammatory cytokines synthesis, distinguished responders from non-responders). The association between suicidal behavior and miRNA processing gene variants was explored by He et al. (2012) by comparing 314 MDD patients and 252 healthy controls. Frequencies of genotypes and alleles showed significant differences between MDD patients and healthy controls in DGCR8 rs3757 and AGO1 rs636832. Variant allele of DGCR8 rs3757 was associated with increased risk of suicidal tendency and improvement response to AD treatment, whereas the variant of AGO1 rs636832 showed decreased risk of suicidal tendency and suicidal behavior. Changes of miRNAs profile expression in the blood serum of 10 MDD patient treated with escitalopram were examined by Bocchio-Chiavetto et al. (Bocchio-Chiavetto et al., 2013). After 12 weeks of AD treatment, thirty miRNAs (28 upregulated; 2 downregulated) in peripheral blood exhibited significant changes in expression. In particular, 13 miRNAs play a crucial role in neurogenesis and synaptic plasticity as well as in coping response to stress. In addition, Li et al. (2013) found decreased BDNF levels associated with unregulated miR-182 in MDD patients compared with controls. Furthermore, Fan et al. (2014) found miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743 upregulated in PBMCs of MDD patients. These miRNAs are involved in several pathways associated with nervous system and brain functions. A confirmation that blood cells might reflect the metabolism of brain cells is presumably related to the study by Wan et al. (2015) according to which miRNA expression profiles were analyzed in CSF and in specimen serum. Overall, 4 miRNAs were altered in both CSF and serum: miR-221-3p, -34a-5p, and let-7d-3p upregulated; miR-451a downregulated. Moreover, Maffioletti et al. (2016) evaluated the expression levels of 1733 mature miRNAs annotated in miRBase v.17, through a microarray technique, in the blood of 20 MD, 20 BD patients and 20 healthy controls. The bioinformatic prediction of the genes targeted by the altered miRNAs (see Table 5) revealed the possible involvement in Wnt signaling pathway, mTOR signaling pathway, ErbB signaling pathway and Insulin signaling pathway for both MDD and BD. Jak-STAT signaling pathway and Ubiquitin mediated proteolysis seem to be altered specifically in MDD patients whereas long-term potentiation, phosphatidylinositol signaling system, neurotrophin signaling pathway and gap junction were specifically altered only in BD patients. He et al. (2016) and Roy and colleagues (Roy et al., 2017b) demonstrated that miR-124-3p, known for targeting genes involved in neural plasticity and coping response to stress, was 3,5-fold increase in serum of MDD patients compared to HC. The levels of this miRNA significantly decreased after eight weeks of AD treatment. Similarly, and in line with other independent clinical trials on MDD subjects, Lopez et al. (2017) conducted a large, randomized placebo-controlled trial of duloxetine collected before and 8 weeks after treatment and found differential expression of miR-146a-5p, miR-146b-5p, miR-425-3p and miR-24-3p. These miRNAs were correlated to the dysregulation of genes involved in MAPK/Wnt signaling pathways. Wang et al. (2018b) found increased levels of miR-19a-3p expressed in PBMC of 12 MDD patients with severe suicidal ideation compared to 12 HC. MiR-19a-3p was upregulated in PFC of depressed subjects died by suicide and linked to the upregulation of TNF-α expression. Liang et al. (2020) recruited 30 patients with MDD and 30 HC subjects, and used TaqMan probes to detect serum exosomal miR-139-5p levels in blood serum, finding a significantly increased level of exosomal miR-139-5p MDD patients. This miRNA is a promising biomarker for diagnosis of MDD. Chen et al. (2020) tried to differentiate bipolar depression (BD) and unipolar depression (UD) according to different miRNA expression level. BD patients showed higher expression level of miR-19b-3p in more severe childhood trauma experience compared to UD patients. miR-19b-3p seems to be involved in the inflammatory pathway dysregulation associated with childhood abuse. Furthermore, childhood maltreatment in UD subjects were associated with higher levels of miR-9 (He et al., 2021). Zhang and colleagues reported that decreased levels of plasma miR-134 might be a biomarker for distinguish major depressed subjects from healthy subjects and bipolar and schizophrenic patients with both sensitivity and specificity above 75 % (Zhang et al., 2020).

Conclusive remarks

Both clinical and preclinical evidence support the eminent role of

Table 5
Clinical studies about the link between circulating levels miRNAs and major affective disorders.

Authors	Dysregulated miRNA	Implicated pathways	Source	Sample	Main findings
Belzeaux et al. (2012)	Has-miR-107, Has-miR-133a, Has-miR-148a, - Has-miR-200c, Has-miR-381, Has-miR-425-3p, Has-miR-494, Has-miR-517b, Has-miR-579, Has-miR-589, Has-miR-636, Has-miR-652, Has-miR-941, Has-miR-1243	HIST1H4E; IL1B; PPT1; TNF-α	Peripheral blood mononuclear cells	16 MDD patients; 13 HC	The main changes in the expression of miRNAs were observed after 2 and 4 weeks of AD treatment. Non responders were identified by a specific core of 6 gene polymorphism.
He et al. (2012)	MiR-124 ↑	Genomic sequencing of miRNA processing variant gene DGCR8 rs3757 and AGO1 rs636832	Peripheral vein blood	314 MDD patients; 252 HC	The variant allele of DGCR8 rs3757 was associated with increased risk of suicidal tendency and better response to AD. The variant of AGO1 rs636832 was linked to lower risk of suicidal tendency, suicidal behavior.
Bocchio-Chiavetto et al. (2013)	Let-7d, let-7e, miR-26a, miR-26b, miR-34c-5p, miR-103, miR-128, miR-132, miR-183, miR-192, miR-335, miR-494, miR-22; miR-132	BDNF, GR, NR3C1, NOS1, growth factors (IGF1, FGF1, FGFR1, VEGFa and GDNF), calcium channels (CACN41C, CACNB4, SLC6A12 and SLC8A3) and neurotransmitter receptors (GABRA4 and 5-HT4)	Blood serum	10 MDD patients (8 drug-naïve from AD; 2 previously treated with St John's worth)	Changes concerning the expression of the mentioned miRNAs were observed after escitalopram treatment.
Li et al. (2013)	MiR-182 ↑	BDNF	Blood serum	40 MDD patients 40 HC	Upregulated miR-182 levels in MDD patients were associated with reduced BDNF expression.
Fan et al. (2014)	MiRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, miRNA-4743 ↑	Pathways related to CNS functions	Peripheral blood; mononuclear cells	81 MDD patients 46 HC	The upregulation of these miRNAs correlated with downstream of genes involved in depressed mood and suicidal behavior.
Wan et al. (2015)	MiR-221-3p, -34a-5p, let-7d-3p ↑, miR-451a ↓	BDNF; SIRT-1	CSF Blood serum	6 MDD patients; 6 HC 32 MDD patients; 21 HC	The mentioned miRNAs were dysregulated in MDD patients
Maffioletti et al. (2016)	Hsa-let-7a-5p, hsa-let-7d-5p, hsa-let-7f-5p, hsa-miR-24-3p hsa-miR-425-3p; hsa miR-140-3p, hsa miR-30d-5p, hsa miR-330-5p, hsamiR-378a-5p hsa-miR-21-3p, hsa-miR-330-3p, hsa-miR-345-5p	Wnt signaling pathway; mTOR signaling pathway; ErbB signaling and Insulin signaling pathways; Jak-STAT signaling pathway and Ubiquitin mediated proteolysis specific for MDD; lLong-term potentiation, phosphatidylinositol signaling system; Neurotrophin signaling pathway; Gap junction specific for BPD	Whole blood	60 subjects, of which 20 with MDD, 20 with BPD and 20 HC	Hsa-let-7a-5p, hsa-let-7d-5p, hsa-let-7f-5p, hsa-miR-24-3p and hsa-miR-425-3p levels were altered in MDD patients. Hsa-miR-140-3p, hsa-miR-30d-5p, hsa-miR-330-5p, hsa-miR-378a-5p and hsa-miR-21-3p were altered in BD patients. Finally, hsa-miR-330-3p and hsa-miR-345-5p were dysregulated in both MDD and BD samples.
He et al. (2016)	MiR-124-3p↑	Stress response; Neural plasticity	Peripheral blood mononuclear cells	32 MDD patients	Significant decline in miR-124-3p levels after 8 weeks of AD treatment.
Roy et al. (2017a)	MiR-124-3p↑	Stress response; Neural plasticity	Blood serum	18 MDD patients	MiR-124-3p was the target for drug development and a biomarker for MDD pathogenesis.
Lopez et al. (2017)	MiR-146a-5p, miR-146b-5p, miR-425-3p miR-24-3p	MAPkinase; Wnt signalling pathways	Whole blood	61 MDD patients treated with duloxetine	After 8 weeks of AD treatment, responders showed a significant downregulation of the implicated miRNAs.
Wang et al. (2018)	miR-19a-3p ↑	TNF-α	Peripheral blood mononuclear cells	12 MDD patients with severe suicidal ideation and 12 HC	Increased TNF-α expression and proinflammatory pattern was found in MDD patients with suicidal ideation.
Liang et al. (2020)	↑miR-139-5p		Blood serum	30 patients diagnosed with MDD and 30 HC	Patients with MDD were accompanied by significantly increased blood exosomal miR-139-5p levels. Exosomal miR-139-5p is a promising biomarker fo the diagnosis of MDD.
Chen et al. (2020)	↓ miR-19b-3p	mTOR FoxO PI3-K/Akt	Blood plasma	7 BD patients 7 UD patients 6 HC	Plasma miR-19b-3p is a potential non-invasive biomarker that might be useful in distinguishing UD from BD. miR-19b3p was predicted to be involved in the pathway of inflammatory dysregulation associated with experiencing early childhood trauma.

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Table 5 (*continued*)

Authors	Dysregulated miRNA	Implicated pathways	Source	Sample	Main findings
Zhang et al. (2020)	↓ miR-134		Blood plasma	100 MDD patients 50 BD patients 50 SZ patients 100 HC	Plasma miR-134 is a potential non-invasive diagnostic biomarker for distinguish MDD from HC (79% sensitivity and 84% specificity) and BPD/SZ (79% sensitivity and 76.5% specificity) subjects.
He et al. (2021)	↑miR-9		Blood plasma	40 unmedicated MDD patients 34 HC	MDD patients showed higher miR-9 levels that were negatively correlated with childhood maltreatment scores and depressive severity. The connectivity between amygdala and prefrontal-limbic circuits might underlie these correlation.

Note: Antidepressant (AD); Protein Argonaut 1 genetic variant rs636832 (AGO1 rs636832); Brain Derived Neurotrophic Factor (BDNF); Bipolar Disorder (BPD); Calcium Channel 41 C (CACN41C); Calcium Channel B4 (CACNB4); Central Nervous System (CNS); DiGeorge syndrome critical region 8 genetic variant rs3757 (DGCR8 rs3757); Epidermal growth factor receptor B (ErbB); Fibroblast Growth Factor 1 (FGF1); Fibroblast Growth Factor Receptor 1 (FGFR1); Gamma-Aminobutyric Acid Type A Receptor Subunit Alpha4 (GABRA4); Glial cell-derived neurotrophic factor (GDNF); Glucorticoid receptor (GR); Healthy controls (HC); histone cluster 1, H4e gene (HIST1H4E); Insuline growth factor 1 (IGF1); Major Depressive Disorder (MDD); Mammalian target of rapamycin (mTOR); interleukin 1B (IL1B); Nitric oxide synthase 1 (NOS1); Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1); Palmitoyl-Protein Thioesterase 1 (PPT1); Sodium- and chloride-dependent betaine transporter 6A12 (SLC6A12); Sodium- and chloride-dependent betaine transporter 8A3 (SLC8A3); SZ, Schizophrenic; Tumor Necrosis Factor-α (TNF-α); Vascular endothelial growth factor A (VEGFa); Wingless-related integration site (Wnt); Serotonin type 4 receptor (5-HT4); Unipolar Depressive Disorder (UD).

miRNAs in the pathophysiology of major affective disorders and suicidal behavior. According to these studies, the gene-environment interaction and epigenetic regulation underlying prominent neuropsychiatric conditions need to be emphasized.

However, we are only at the beginning of a fascinating journey. MiRNAs may play a prominent role as gene expression regulators critically affecting brain development. Based on the main findings of this overview, most of the identified miRNAs are expressed in the brain, where they are able to regulate neurogenesis, neuroplasticity, and other fundamental neural processes (Serafini et al., 2014, 2012). A better understanding of the complex mechanisms regulated by miRNAs in major affective disorders might help clinicians to clarify the differential vulnerability to stress, improve diagnostic abilities, enhance the prediction of response to specific treatments options in line with the new era of precision psychiatry. Either the earlier diagnosis as well as the treatment selection represent two significant goals of precision psychiatry based on the development and validation of reliable biomarkers in this field. Future studies should further investigate the neurobiological mechanisms underlying the association between miRNA expression alterations and the pathophysiology of affective disorders, in order to characterize a possible association with specific psychopathological features.

In the new era of precision medicine, miRNAs are rapidly advancing our scientific understanding contributing to the science of the future which will be to provide an integrated perspective underlying complex and disabling conditions such as major affective disorders and suicidal behavior.

Declaration of Competing Interest

The authors (Alice Trabucco, Giovanni Corsini, Andrea Escelsior, Andrea Amerio, Andrea Aguglia, Henry Nasrallah, Mario Amore) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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