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Title: Role of miRNAs in depression vulnerability or resilience: novel targets for preventive strategies?

Authors: Nicola Lopizzo[1,3], Valentina Zonca [1,2,3], Nadia Cattane[1], Carmine Pariante[2] and Annamaria[1,2,*] Cattaneo

Affiliations:

[1]Biological Psychiatry Unit, IRCCS Fatebenefratelli S. Giovanni di Dio, Brescia.

[2]Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College, London.

[3] Co-first author

* Corresponding author:

Dr. Annamaria Cattaneo

Biological Psychiatry Unit, IRCCS Fatebenefratelli Institute Via Pilastroni 4, 25125 Brescia, Italy

Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College London, London, Coldharbour Lane, SE5 9NU, London, UK

Email: annamaria.cattaneo@kcl.ac.uk;

Email: acattaneo@fatebenefratelli.eu

Abstract:

In the last years, researchers have shown how stress is strictly involved in the onset and development of depression, principal due to the mechanism of dysregulation of the Hypothalamic-pituitary-adrenal axis. Stressful experiences during the prenatal period or during the first years of life can affect the brain developmental trajectories leading to an enhanced vulnerability of developing several psychiatric and neurodevelopmental disorders later in life, but not all the subjects exposed to stressful experiences suffer from such illnesses . For this reason, during the last decades, researchers have focused their attention on the identification of stress coping mechanisms, able to explain the resilience or vulnerability of developing psychiatric diseases, such as depression.

MiRNAs represent one of the epigenetic mechanisms associated with long-lasting detrimental effects of stress and they have been proposed as possible biomarkers able to identify subjects at high risk to develop depression and to predict the treatment response.

The focus of this review is to evaluate the current state of the art related to the relationship between miRNAs, stress vulnerability and depression by discussing, both in rodents as well as in humans, how miRNAs can mediate the long-lasting effect of stress and how changes in miRNAs expression can also be involved in the response to pharmacological treatments.

To this purpose, different combinations of relevant keywords were used to search references in PubMed database.

Studies, both in humans and in animals show several clues that give an idea of the possible mediation of epigenetic mechanisms in the vulnerability and/or resilience related to the pathology. For this reason, the evaluation of miRNAs expression in peripheral blood and tissues might be a promising breakthrough in the diagnosis and prevention of depression and in the identification of novel targets for preventive pharmacological or non-pharmacological strategies.

Sommario

1. Stress, Depression and miRNAs

It is well known that adverse experiences during the prenatal period or during the first years of life can affect the brain developmental trajectories leading to an enhanced vulnerability of developing several psychiatric and neurodevelopmental disorders later in life (Lockhart et al. 2018). Indeed, early life stressful experiences represent an important clinical risk factor for the future development of altered behaviours and psychiatric disorders (Cirulli et al. 2009; Fryers and Brugha 2013; Syed and Nemeroff 2017). However, the molecular mechanisms underlying the long-lasting effects of stress are poorly understood, and likely interact with genetic and biological factors throughout the lifespan, a mechanism also known as gene X environment interaction (McEwen 2012; Holmes and Singewald 2013; Karatsoreos et al. 2013). In this context, epigenetic mechanisms, such as DNA methylation and microRNAs (miRNAs), have been widely described to mediate the effect of these stressful experiences and to be involved in the vulnerability of depression (Serafini et al. 2014; Januar et al. 2015) as well as for other stress-related mental disorders (Klengel and Binder 2015; Nestler et al. 2016). Indeed, they act by inducing long-lasting alterations in the expression of key genes and pathways (Menke 2014), that in turn may contribute to the development of the pathology.

MiRNAs, as mentioned before, represent together with DNA methylation, one of the epigenetic mechanisms associated with the long-lasting detrimental effects of stress. MiRNAs are small non-coding RNA molecules (21-24 nucleotides), recognized as one of the fundamental factors involved in the post-transcriptional regulation of gene expression. Indeed, it has been estimated that they are able to modulate up to 60% of protein-coding genes in humans (Catalanotto et al. 2016), generally repressing the expression of their target mRNAs (Bushati and Cohen 2007; Friedman et al. 2009; Rao et al. 2013). The fine-tuning of gene expression by miRNAs is usually regulated through the binding to the 3'UTR of mRNA, leading to mRNA degradation or translational repression (Bartel 2004). Also coding domain sequence and 5'UTR are targeted by miRNAs with consequent regulatory effects on gene expression (Brummer and Hausser 2014; Catalanotto et al. 2016). Because of their ubiquitous role in gene regulation, they are involved in many physiological processes, such as cell proliferation, differentiation, apoptosis and development. A dysregulation in the miRNAs' machinery has been related to several pathological conditions, including neuropsychiatric and neurodevelopmental disorders (Ha 2011; Xu et al. 2012; Maffioletti et al. 2014).
MiRNAs have been proposed as non-invasive candidate biomarkers that would allow the early identification of individuals at high-risk of developing depression and of those subjects who are more resistant to the pharmacological treatment. Indeed, miRNAs play an important regulatory role in all the biological pathways that are dynamically triggered by stress and they also represent one of the fastest and most dynamic response mechanism that can regulate gene transcription and protein translation in response to stress (Ebert and Sharp 2012).

This review focuses on the relationship between miRNAs, stress vulnerability or resilience and depression by discussing, both in rodents as well as in humans, how miRNAs can mediate the long lasting effect of stress on depression vulnerability or resilience and how changes in miRNAs expression can also mediate the

response to pharmacological treatments. To this purpose, we searched different combinations of keywords, such as “miRNA”, “stress”, “childhood trauma”, “depression”, “vulnerability”, “resilience”, “mouse”, “rats”, “animal models”, “biomarkers”, “antidepressant” and “antidepressant response”, using PubMed searching database references. In the following sections, the identified studies are reported in tables and the most important studies will be discussed.

2. Effect of stress on miRNAs biogenesis

Before discussing how stress can induce changes in the levels of miRNAs and of their target genes and signalling, we will introduce how stress can affect the entire process involved in the biogenesis of miRNAs.

During the last years, several studies have investigated the exact role of miRNAs, from their production to their role as regulators of gene expression, in order to understand the key steps that can be affected by stress and thus involved in the pathogenesis of several psychiatric disorders, especially stress related disorders, like depression.

MiRNAs are encoded as precursor-miRNAs (pre-miRNAs), long primary transcripts with a cap structure at the 5’ end and polyadenylation at the 3’ end. The processing of the pre-miRNAs starts by the cellular endonuclease Drosha with the microprocessor complex subunit DGCR8/Pasha. The pre-miRNA is cleaved by the endoribonuclease Dicer in cytoplasm, producing a short double stranded miRNA duplex, which is then processed in a mature miRNA. Subsequently, it is incorporated in the RNA-induced silencing complex, constituted by the components of the Argonaute family protein (Wahid et al. 2010; Nakanishi 2016). Mature miRNAs activate or repress the Wnt pathway at multiple levels by targeting Wnt ligand/receptor and ligand/ receptor associated proteins, β-catenin. Wnt activation increases the expression of miRNAs through the binding of β-catenin to transcription factors, which bind to promoter regions to activate transcription (Ghahhari and Babashah 2015; Peng et al. 2017). β-catenin protein plays a key protective role in stress conditions, upstream miRNA synthesis, through the control of the enzyme Dicer1 also according to a recent study conducted by Dias and co-workers (2014), and indeed, the presence of lower levels of Dicer1, as consequence of stress exposure, has been also associated with an enhanced vulnerability to stress (Lim et al. 2011; Mori et al. 2012; Dias et al. 2014).

For example, Wingo and collaborators (2015) investigated the impact of Dicer1 regulation in patients with post-traumatic stress disorder and with comorbid depression, reporting reduced levels of Dicer1 in patients as compared to controls, an effect that was replicated in other two independent cohorts (Wingo et al. 2015). Interestingly, several proteins involved in β-catenin activity control, including the enzyme Glycogen synthase kinase 3, have been found altered in depressed patients (Jope and Roh 2006; O’Brien and Klein 2007).

Similarly, He and colleagues (2012) reported an association between genes involved in miRNAs biogenesis with depression. Indeed, they investigated several single nuclear polymorphisms within several genes including DiGeorge syndrome chromosomal region 8 (DGCR8), Argonaute1 (AGO1) and Gem-Associated Protein4 in 314 depressed patients and 252 healthy controls and found that genetic variants within DGCR8 (rs3757) and AGO1 (rs636832) increased the risk for depression (He et al. 2012).

3. Role of miRNAs in stress response and neuropathological conditions in humans

The activation or the inhibition of transcription is often coordinated by the action of several miRNAs that act together in clusters (Catalanotto et al. 2016). Although several genes are responsive to a single miRNA and an individual gene can be targeted by several miRNAs, the ideal strategy would be to study the coordinated action of all the miRNAs and their target genes, the direction of the modulation of each miRNA and target gene, as well as to analyse the pathways and the complex networks in which they are involved (Carroll et al. 2013).

Studies on the changes in miRNAs levels in association with stress exposure or with depression in humans are only few in the literature and below here we reported and discussed the main studies conducted in post-mortem brains, in peripheral blood and in sperm samples. In Table 1 we reported all the studies showing alterations in miRNAs levels in depressed patients or in subjects exposed to stress. We used as input keywords for Pubmed "miRNAs", "Stress", "Childhood Trauma", "Depression", "Resilience", "Vulnerability".

3.1 Studies on post-mortem brains

Most of the studies in the literature are focused on the possible role of miRNAs in driving the effect of stress exposure on depression vulnerability. For example, Smalheiser and collaborators (2012) investigated a miRNAs network in post-mortem brains of antidepressant-free depressed suicide patients by using multiplex RT-PCR, identifying a network of miRNAs able to target several genes, which have been already demonstrated to be involved in depression vulnerability. Indeed, they found that miRNAs expression was overall significantly down-regulated in cases versus controls, with a particular effect on 21 miRNAs, which have a common seed region (Smalheiser et al. 2012). Among the predicted targets of these 21 altered miRNAs, they found estrogen receptor alpha (ESR1), which resulted to be targeted by 3 different down-regulated miRNAs (miR-148b, miR-301a, miR-496). Interestingly, ESR1 has been recently associated with resilience to depression (Lorsch et al., 2018). Moreover, among all the validated target genes of the 21 modulated miRNAs they also found the DNA Methyltransferase 3 Beta (targeted by miR-148b), the Vascular endothelial growth factor A (VEGF-A) (targeted by miR-20b, miR-20a, miR-34a, miR-35b-5p), and the B-cell lymphoma 2 (targeted by miR-34a) genes, that interestingly have been all already associated with depression vulnerability (Smalheiser et al. 2012).

Maheu and colleagues (2015) analysed whether (and which) miRNAs can alter the neuronal response to Glial Cell Line-Derived Neurotrophic Factor (GDNF), which was previously related with coping stress abilities and associated with the neuroplasticity related mechanisms, and was also found reduced in depressed patients (Uchida et al. 2011; Lin et al. 2015). In particular the authors showed an inhibitory action of a specific miRNA, the miR-511, on the GDNF receptors expression (GFRα1a and GFRα1b) in depressed suicidal subjects' post-mortem brains (Maheu et al. 2015). Their results showed that this inhibition occurs specifically and independently on the GFRα1a receptor, suggesting that the changes induced in GDNF signalling can be considered more in changing the quality, rather than the quantity, of GDNF signalling.

In addition, miR-135a and miR-124-3p have been investigated as possibly involved in depression vulnerability (Issler et al. 2014; Roy et al. 2017). Issler and collaborators (2014) reported lower levels of miR-135a in the raphe nuclei of suicide victims as compared to control subjects and they also reported the same reduction at peripheral level (in plasma samples); in parallel, they also demonstrated alterations in miR-135a target genes involved in the regulation of Serotonin (5-HT) neuron-related genes such as the 5-HT transporter, SLC6A4, and the 5-HT receptor, HTR1A, suggesting a role for miR-135a as a potential blood biomarker for depression vulnerability (Issler et al. 2014). Another miRNA that has been implicated in depression vulnerability is the miR-124-3p, which Roy and colleagues (2017) found increased in the Pre-Frontal Cortex of post-mortem brains of depressed patients as compared to controls. They also found reduced expression of miR-124-3p target genes Glutamate receptor 3, Glutamate receptor 4, and Glucocorticoid receptor (NR3C1), which are genes all involved in stress response and neuroplasticity (Roy et al. 2017).

MiR-218, which targets Netrin-1 guidance cue receptor Deleted in Colorectal Cancer (DCC), has been proposed as a new epigenetic marker of stress vulnerability. Briefly, Torres-Berrio and collaborators (2017) investigated the mechanism of co-expression of DCC and miR-218 in pyramidal neurons of human pre-frontal cortex. The expression of miR-218 and DCC was quantified in post-mortem prefrontal cortex tissue samples obtained from antidepressant-free depressed subjects who committed suicide and sudden-death controls, using Real Time PCR and immunofluorescence. They found increased DCC and reduced miR-218 expression levels in the prefrontal cortex of depressed subjects in line with the expected inverse relationship between miRNAs and mRNA levels of target gene. Therefore, this imbalance between miR-218 and its target DCC levels could be a key mechanism of susceptibility to stress (Torres-Berrio 2017).

3.2 Studies on Peripheral Blood, Cerebrospinal fluid and sperm samples

As compared to the studies conducted in post-mortem brains, more lines of evidence on peripheral blood from subjects exposed to stressful events or from depressed patients are available in the literature.

One of the first studies has been published by Fan and collaborators (2014) who identified changes in 26 miRNAs in peripheral blood mononuclear cells obtained from 3 depressed patients compared to 3 control subjects using miRNAs microarray expression profiling. The authors validated the microarray results using Real Time PCR in an enlarged cohort of 91 depressed patients and 46 control subjects matched by age and gender. All the 26 miRNAs were upregulated in depressed patients except for miRNA-338 and, among these 26 miRNAs, miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743 demonstrated a significant difference. Investigating more in detail the pathways in which the significant altered miRNAs were involved, the authors observed a particular enrichment in pathways such as axon guidance, glutamatergic synapse, Wnt signalling pathway, ErbB signalling pathway, mTOR signalling pathway, VEGF signalling pathway and long-term potentiation, in line with literature data that suggest a possible involvement of these systems in the mechanisms related to depression development (Voleti and Duman 2012; Fan et al. 2014; Abelaira et al. 2014).

MiRNAs have been also investigated with the aim to identify a possible association with depressive symptomatology. For example, Wang and collaborators (2015) identified the miR-144-5p whose baseline

levels were reduced in depressed patients as compared to controls and were inversely correlated with MADRS-S scores, suggesting miR-144-5p as a possible biomarker associated with the severity of depression (Wang et al. 2015).

Another miRNA that could be implicated in the physiopathology of depression is miR-16, via the modulation of serotonin transmitter system in the brain (Song et al. 2015). In particular miR-16 levels in the CSF from depressed patients were significantly lower than those in controls; moreover, CSF miR-16 was negatively correlated with Hamilton scores and positively associated with CSF serotonin levels, suggesting that the measurement of this miRNA in the CSF could be a promising biomarker for mood changes (Song et al. 2015).

Alterations in miR-132 and miR-182 have been associated with depression vulnerability via the modulation of Brain-Derived Neurotrophic Factor (BDNF) that plays an essential role in neurodevelopment and neuroplasticity and whose levels have been found reduced at peripheral and central level in depressed patients as compared to controls. Li and collaborators (2013) measured serum BDNF levels and a panel of miRNAs that target BDNF in 40 depressed patients versus 40 healthy controls, reporting lower BDNF levels in association with depression, whereas the levels of miR-132 and miR-182 were significantly increased (Li et al. 2013). A reduction in BDNF protein levels has been also suggested to promote the development of depression and its treatment resistance by several studies (Lee and Kim 2010; Ihara et al. 2016).

A recent work of Gururajan and collaborators (2016) showed that let-7b and let-7c can regulate the expression of 27 genes in the PI3K-AKT-mTOR signalling pathway, which has previously been reported to be deregulated in depression. Indeed, the expression of the miRNA let-7b and let-7c was found significantly decreased in a group of treatment-resistant depressive patients compared with control subjects (Gururajan et al. 2016).

The impact of miRNAs on depression vulnerability has been also evaluated from a genetic point of view; indeed, Liang and colleagues (2015) have investigated the possible contribution of single nucleotide polymorphisms in the promoters of let-7 family in the mechanisms of vulnerability for depression development, by genotyping 237 depressed patients and 296 healthy controls. The let-7 family has been the first to be discovered in humans with well-known key roles in neurogenesis and synapse formation (Rehfeld et al. 2015) and a possible involvement in depression development (Maffioletti et al. 2016). The authors showed that both the rs10877887CC and the rs13293512CC let-7 genotypes increased the risk for depression onset (Liang et al. 2015).

Only a few studies have investigated the possible effects of stressful life events on miRNAs modulation in humans. Among them, Volk and colleagues (2016) suggested an important role for miR-15a in the development of coping strategies versus stressful exposures. Indeed, they analysed miR-15a expression levels in RNA samples from peripheral blood cells of young healthy male subjects following oral administration of the glucocorticoid receptor agonist dexamethasone, reporting a significant upregulation of miR-15a at 3- and 6-hours post-treatment, an effect that interestingly was also present in peripheral blood cells of control subjects exposed to childhood trauma as compared to non-exposed individuals. Given the previous evidence of the key role of the Hypothalamic-Pituitary-Adrenal (HPA) axis and of childhood trauma in the development of depression (Juruena 2014; Keller et al. 2017; Juruena et al. 2018), the authors' findings indicate that miR-15a is potentially regulated by the activation of the stress hormone system in

humans and it is involved in stress vulnerability and in the possible correlated development of psychopathology (Volk et al. 2016).

Recently, Dickson and collaborators (2018) have also investigated the effects of childhood trauma on miRNAs levels using a different biological matrix, the sperm of voluntary healthy subjects. As a first-level screen to find candidate miRNAs whose expression in sperm correlates with Adverse Childhood Experience (ACE) score, they selected sperm samples from five men with the highest ACE scores (≥4) and five with the lowest (0–1) and performed miRNAs array analysis on each sample. Multiple members of the miR-34/449 family showed pronounced reduction in the group of subjects with highest ACE score, in particular miR-449a and miR-34c (Dickson et al. 2018).

In conclusion, to date, literature data in human studies show several clues that give an idea of the possible contribution of epigenetic mechanisms in the vulnerability and/or resilience related to depression. Studies have focused more on significant changes in miRNAs levels and their targeting genes in depressed patients versus controls, taking only partially into account the possible effects of stressful life events and the related coping strategies.

microRNA/Gene	***Methods***	***Principal Findings***	***Reference***
DICER1	Genome-wide β-catenin enrichment mapping	β-catenin could have a protective role through miRNA production.	*Dias et al. 2014*

DICER1	Genome-wide differential gene expression profiles in blood of PTSD and Depression cases versus controls with no PTSD and no depression.	DICER1 plays a role in molecular mechanisms of PTSD and Depression through the DICER1 and subsequent miRNA regulation pathway.	*Wingo et al. 2015*
DGCR8, AGO1 and GEMIN4	High-resolution melting and Real time PCR	Variants of DGCR8 rs3757 and AGO1 rs636832 increased depression risk.	*He et al. 2012*
Panel of 21 miRNAs	Multiplex RT-PCR	Overall miRNA expression was significantly down-regulated in depressed suicide subjects versus control subjects.	*Smalheiser et al. 2012*
miR-511, GDNF	Quantitative Real-Time PCR, miRNA transfections, immunoblotting and immunochemistry	An important role for GDNF in depression, in particular the fine regulation by miRNAs of isoform-specific GFRα1 receptor in shaping neuronal responses to this neurotrophin.	*Maheu et al. 2015*
miR-135a	Western Blot and Real-time PCR	miR135a levels in total blood of depressed human patients were reduced compared to those of healthy controls.	*Issler et al. 2014*
miR-124-3p	qPCR	Significant increase in the expression of miR-124-3p in depressive group, comparing post-mortem brains of depressive subjects and control subjects.	*Roy et al. 2017*
miR-218, DCC	Real-Time PCR and DCC immunofluorescence	miR-218 may be a switch of susceptibility versus resilience to stress-related disorders.	*Torres-Berrio et al. 2017*
miR-26b, miR-1972, miR-4485, miR-4498, miR-4743	qRT-PCR	Expression levels of 5 miRNAs were significantly upregulated in depressed patients compared to healthy controls.	*Fan et al. 2014*
miR-144-5p	Real-time PCR	Plasma miR-144-5p levels in depressive patients were significantly lower than in healthy controls.	*Wang et al. 2015*
miR-16	qRT-PCR	CSF miR-16 decrease in drug-free depressive patients compared to control subjects.	*Song et al. 2015*

miR-132, miR-182	Real-Time PCR, ELISA	Levels of miR-132 and miR-182 were crucial for BDNF regulation levels.	*Li et al. 2013*
miR-15a	Real-time PCR and NGS sequencing (MiSeq)	Increased levels of miR-15a in blood of subjects exposed to childhood trauma or to the oral administration of Dexamethasone.	*Volk et al. 2016*
Let-7 family	Polymerase chain reaction-restriction fragment length polymorphism and DNA sequencing assays	rs10877887 and rs13293512 polymorphisms in let-7 family are related to an increase risk to depression onset and worsening.	*Liang et al. 2015*
Let-7b, let-7c	qRT-PCR	Let-7b and let-7c baseline expression decreased in treatment-resistant depressive patients compared with controls.	*Gururajan et al. 2016*
miR-449a, miR-34c	Microarray analysis and qReal-Time PCR	miR-34/449 dysregulation in sperm of subjects exposed to trauma.	*Dickson et al. 2018*

Table 1. Summary of the studies showing alterations in miRNAs levels in depressed patients or in subjects exposed to stress.

4. Role of miRNAs in the mechanisms underlying stress vulnerability and stress resilience

As we have already mentioned, stress is an important risk factor for the development of several psychiatric diseases, in particular depression (Tost 2015). The American Psychological Association (APA) has defined stress as "the physiological or psychological response to internal or external stressors" (APA 2018). However, the response and the impact of stress on each individual might be different, as it is not only attributable to the exposure to stressful events through lifetime, rather to a plethora of risk factors, including the individual genetic background, the environment and how these two factors interact with each other, a mechanism also known as Gene X Environment interaction.

Based on this, although traumatic life events, especially those occurring early in life or during adolescence, represent an important clinical risk factor for the future vulnerability for depression, not all the exposed individuals develop stress-related psychiatric disorders, but some of them acquire coping strategies and become resilient (Wu et al. 2013; Pfau and Russo 2015). For this reason, the identification of molecular mechanisms and of biomarkers associated with vulnerability or resilience will help in the identification of subjects at high risk; monitoring and preventive programmes could be then proposed to the identified high-risk individuals to minimize their susceptibility of developing psychopathology later in life.

On the other hand, the identification of mechanisms underlying resilience might be useful for the identification of processes that confer "protection" versus stressful exposures, thus will be useful for the discovery of novel targets for the development of new drugs and preventive strategies. In this context, miRNAs might be a fundamental tool to recognize vulnerable or resilient subjects permitting to high-risk subjects to benefit from such preventive therapies.

Unfortunately, up to now, most of the studies reported in literature analyses the effect of stress without focusing on potential differences in relation to stress vulnerability or resilience,. Accordingly, in this paragraph we will show the main findings regarding the effect of stress on miRNAs levels (Table 2), mentioning also the latest research on distinct miRNAs changes in relation to stress vulnerability and stress resilience (Table 3). To do this, we searched in Pubmed studies using the keywords: "stress" and "miRNAs" and we included only findings related to effect of stress on miRNAs modulation. Within the 11 relevant studies, all reported in Table 2, in the present paragraph we will deeply discuss only those that are focused on miR-124 and miR-16, as they are the most investigated miRNAs in the context of stress.

One of the first study showing how stress affects miRNAs comes from Bahi and colleagues in 2014 which investigated the modulation of miR-124a in rats exposed to chronic social defeat stress, which consists of placing the animal in the home cage of an unfamiliar rat and in allowing them to interact until the intruder shows a defeat position for approximately 3 seconds. The authors reported higher levels of miR-124a in the hippocampus of stressed rats, whereas no differences were observed in their prefrontal cortex as compared to matched controls (Bahi et al. 2014). Interestingly, miR-124 directly targets and thus modulates the expression of the BDNF, which is known to modulate neurogenesis in the hippocampus and it is also involved in the pathophysiology of depression (Castren et al. 2007; D'Sa and Duman 2002; Duman and Monteggia 2006). In line with the presence of an up-regulation of miR-124a, Bahi and colleagues also found reduced BDNF levels in the hippocampus of the same animals supporting that BDNF gene expression can be

modulated by changes in miR-124a. The authors suggested that miR-124a might participate in the induction of depressive-like behaviour through the regulation of the BDNF gene expression (Bahi et al. 2014). In line with these results, the study of Cao and colleagues, showed that miR-124 is up-regulated in the hippocampus of rats exposed to a chronic unpredictable stress, suggesting again a role of miR-124 in depressive-like behaviour induced by stress (Cao et al. 2013).

In addition, miR-16 has been suggested to participate in the mechanisms underlying stress response through the regulation of its target gene BDNF (Bai et al. 2012). The down-regulation of BDNF in the hippocampus of rodents has been associated with depressive like behaviour caused by different stress paradigms (Larsen et al. 2010). For instance, rats exposed to maternal deprivation and chronic mild stress, when compared to controls, exhibited a depressive-like behaviour which paralleled the presence of lower BDNF levels in the hippocampus and of an up-regulation of miR-16 expression levels (Bai et al. 2012).

Now, we will discuss those studies showing changes in miRNAs expression levels related to stress vulnerability and resilience. Table 3 provides a summary of miRNAs associated with stress vulnerability and resilience of developing a psychiatric disease in animals. To this purpose, we searched in Pubmed for animal studies using the keywords “stress”, “miRNAs”, “vulnerability” and “resilience” and we found 8 relevant studies.

In 2015, Chen and collaborators were one of the first researchers looking at vulnerability and resilience as different and distinct responses to stress. Animals were behaviourally tested and divided into the vulnerable or resilient group, depending on the delay latencies they used to display the defeat position: rats showing an average of latency score <300 s were classified as short latency rats and these animals represented the vulnerable group. On the other hand, the resilient group was represented by the long latency rats, which displayed a latency score >300 s. MicroRNAs profiling on blood collected before the stress exposure showed four miRNAs significantly decreased in rats that developed a vulnerable phenotype: miR-24-2-5p, miR-27a-3p, miR-30e-5p and miR-362-3p. Conversely, after exposure to chronic stress, the expression levels of another panel of miRNAs (miR-139-5p, miR-28-3p, miR-326-3p and miR-99b-5p) were lower in animals showing a resilient phenotype (Chen et al. 2015).

Whether a few studies analysed the entire profile of miRNAs by using ‘omics approaches, others focused the attention on single and specific miRNAs, such as miR-124 and miR-16 (Xu et al. 2017; Higuchi et al. 2016; Zukarew et al. 2016). For example, Xu and collaborators reported that rats exposed to a chronic unpredictable mild stress or treated with dexamethasone during adolescence showed an up-regulation of miR-124 expression levels in the basolateral amygdala as compared to non-stressed animals (Xu et al. 2017).

The same miRNA was found reduced in the hippocampus of mice exposed to chronic ultra-mild stress, which consists of one-week period of repeated mild stressful events which developed depression-like behaviour, whereas the antidepressant imipramine (TCA) reverted the effect of stress (Higuchi et al. 2016). In the same study, the overexpression of the viral-mediated miR-124 in murine hippocampal neurons conferred behavioural resilience to chronic mild unpredictable stress, whereas the infusion of the anti-miR-124 was able to drive the development of enhanced vulnerability to a stress paradigm, supporting that the modulation of this miRNA can be helpful in discriminating between a stress resilient or a vulnerable phenotype. However, these results are in contrast with the increased expression levels of miR-124 in stressed

animals reported in the previously described studies (Xu et al. 2017; Bahi et al. 2014; Cao et al. 2013). These discrepancies might be due to different animal species, to the stress paradigm and to their interactions. For this reason, further studies are required to identify how the interaction between genes and environment can modify the expression of small non-coding RNAs and their role in depression-like behaviour.

MiR-16 represents another miRNA which has been investigated in relation to stress response. It has been shown to be a key player in the hippocampal neurogenesis and a negative regulator of serotonin transporter (SERT) levels in raphe neurons after fluoxetine treatment (Baudry et al. 2010; Launay et al. 2011). Zurawek and colleagues showed an up-regulation of miR-16 expression levels in serum samples of resilient rats after one week of chronic mild stress paradigm as compared both to animals that developed an anhedonic-like phenotype and also to control animals (Zurawek et al. 2016). Furthermore, after 7 weeks of CMS, anhedonic-like animals showed a significantly down-regulated expression of miR-16 in the ventral tegmental area (VTA) and in the hippocampus as compared to control and resilient rats. The authors observed a steady increase of miR-16 levels from the 1st week to the 6th and 7th week of chronic mild stress paradigm, whereas no fluctuations were seen in the control or anhedonic-like animals during the entire stress paradigm period, suggesting an inadequate or insufficient copying response of vulnerable rats compared to controls (Zurakew et al. 2016).

Besides miR-124 and miR-16, other miRNAs have been associated with resilience and/or vulnerability to stress, such as miR-9, miR-326 and miR-504. Zhang and colleagues investigated the role of miRNAs as possible mediators of the long-lasting effects of early life stress exposures on enhanced susceptibility to chronic stress in adulthood. Rats were exposed to maternal deprivation for the first 14 days of life and then daily exposed to a chronic unpredictable stress from week 10; a group of animals was also treated with escitalopram from week 14 with a daily 4-weeks intraperitoneally infusion. MiR-9 was found to be down-regulated in the striatum of both rats exposed to maternal deprivation with or without exposure to chronic mild stress, whereas miR-326 were down-regulated only in rats exposed to chronic mild stress, suggesting that only miR-326 is sensitive to stress in adulthood. Furthermore, escitalopram did not normalize the decreased levels of miR-9, whereas alterations in miR-326 levels were reverted by 4-weeks of treatment. The authors suggested that maternal deprivation enhanced the development of depression-like behaviours and increased resistance to escitalopram treatment in rats by promoting a down-regulation of miR-9, whereas miR-326 could represent a new target for antidepressant drugs (Zhang et al. 2015). This study is in line with the previous findings showing the presence of an up-regulation of miR-504 which paralleled a down-regulation of dopamine receptor 2 (DRD2) in rats' nucleus accumbens, in association with enhanced vulnerability to stress in adulthood in rats exposed previously to maternal deprivation (Zhang et al. 2013).

Lastly, Pearson-Leary and colleagues identified miR-455-3p and miR-30e-3p as involved in the development of stress copying strategies in rats exposed to chronic social defeat stress. The rats were exposed to social defeat for 7 days and then behaviourally tested to identify vulnerable or resilient animals; interestingly, increased miR-455-3p levels were specifically observed in the ventral hippocampus (vHPC) of resilient mice, whereas an increase in miR-30e-3p levels was observed in vulnerable mice. Pathway analyses identified inflammatory and vascular remodelling pathways as enriched by genes targeted by these

microRNAs, suggesting that inflammatory processes and vascular remodelling in the vHPC, might be directly related to the development of vulnerability to stress (Pearson-Leary et al. 2017).

miRNAs modulated by stress exposure		
miRNA	***Stressful Paradigm***	***References***
miR-134	Chronic unpredictable mild stress	*Yu et al. 2018*
miR-9-5p *miR-128-1-5p* *miR-382-5p* *miR-16-5p* *miR-129-5p* *miR-219a-5p*	Chronic mild stress	*Buran et al. 2017*
miR-135a *miR-16*	Inescapable stress	*Liu et al. 2017*
miR-124	Chronic social defeat Chronic unpredictable mild stress	*Bahi et al. 2014* *Cao et al. 2013*
miR-17-92		*Jin et al. 2016*
Several known miRNAs	Chronic unpredictable mild stress	*Ma et al. 2016*
miR-383 *miR-764*	Chronic unpredictable mild stress	*Duan et al. 2016*
16 miRNAs	Electro-acupuncture	*Duan et al. 2016*
miR-10B	Chronic unpredictable stress Sleep deprivation	*Jiang et al. 2015*
miR-16	Maternal deprivation and unpredictable stress	*Bai et al. 2012*
miR-34c	Acute restraint stress and chronic social defeat stress	*Haramati et al. 2011*

Table 2. List of studies reporting miRNAs modulated by stress exposure.

miRNAs involved in stress resilience and vulnerability		
miRNA	***Stressful Paradigm***	***References***
miR-455-3p *miR-30e-3p*	Chronic social defeat	*Pearson-Leary et al. 2017*
miR-124	Chronic unpredictable mild stress Chronic ultra-mild stress	*Xu et al. 2017* *Higuchi et al. 2016*
miR-16	Chronic mild stress	*Zukarew et al. 2016*
miR-24-2-5p *miR-27a-3p* *miR-30e-5p* *miR-362-3p* *miR-139-5p* *miR-28-3p* *miR-326-3p* *miR-99b-5p*	Chronic social defeat	*Chen et al. 2015*
miR-9 *miR-326*	Maternal deprivation Chronic unpredictable stress	*Zhang et al. 2015*
miR-504	Maternal deprivation	*Zhang et al. 2013*

Table 3. List of studies reporting involvement of miRNAs in the mechanisms associated with resilience and/or vulnerability to stress.

5. Antidepressant drugs and miRNAs

Antidepressant research is currently booming as consequence of the avowal of the burden of depression that is one of the most common medical condition worldwide and the leading cause of disability (World Health Organisation, WHO, 2018). The Guidelines for the treatment of depression indicate as first-line treatments the selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), and other antidepressant drugs including agomelatine, bupropion, mirtazapine and vortioxetine (Mora et al. 2018; Kennedy et al. 2016). Furthermore, approximately a third of depressed patients treated with first line antidepressants report low or absent symptomatology improvement, ending up with dropping out the therapy, or leading to unhealthiest consequences, such as the worsening of symptomatology and even suicide. With the aim of improving treatment response and reducing the burden of depression worldwide, researches are focused on the identification of peripheral biomarkers able to predict the treatment response or the onset of side effects.

In this context, giving the possible role of miRNAs in the pathogenesis of depression, a growing body of evidence has suggested that changes in miRNAs expression may participate not only in the development of the disease, but also in the efficacy of antidepressant treatment. Thus, miRNAs could represent useful biomarkers associated with the disease status and that can predict the treatment response. In the following paragraphs, we will review studies showing an association between changes in miRNAs expression and antidepressant drug response. A summary of all the studies on miRNAs and treatment response in humans are provided in Tables 4, whereas those performed in animal models are shown in Table 5.

5.1 Human studies

Despite the efforts in the identification of predictors for the antidepressant response and the growing evidence of a possible application of miRNAs, poorly has been discovered in humans. Several miRNAs have been found associated with depression, but only a few studies have identified miRNAs as possible predictors of the antidepressant response. In Table 4 we presented all the clinical studies focused on the antidepressant drug response and miRNAs modulation in depressed patients. To identify the mentioned studies, we searched in Pubmed by using the keywords: “miRNAs”, “antidepressants”, “antidepressant response” and “biomarker”. We found 19 relevant studies and in the current paragraph we will focus on the most investigated miRNAs:miR-1202, miR-16 and miR-124.

MiRNA-1202, a brain specific miRNA, regulates the glutamate metabotropic receptor 4 (GRM4) that is involved in the glutamatergic, dopaminergic, GABAergic and serotoninergic transmission (Pilc et al. 2008), due to its pre-synaptical location at both glutamatergic and non-glutamatergic synapses (Bradley et al. 1996). Therefore, GRM4, in addition to regulate the glutamatergic transmission, might act as pre-synaptic regulator for the release of other neurotransmitters (Cartmell 2000). Due to its involvement in several biological processes which have been associated with both the depression development as well as the drug response (Lopez et al. 2014), the miR-1202 has been proposed as a novel potential target for the development of new antidepressant compounds (Davis et al. 2012, 2013). In this context, Lopez and colleagues showed reduced miR-1202 levels in post-mortem brains, specifically in the prefrontal cortex, of depressed patients without a

history of antidepressant treatment compared to depressed subjects treated with antidepressant drugs. The role of miR-1202 in the mechanisms of action of antidepressant drugs has been also investigated in neural precursor cells (NPCs), which have been treated with citalopram (SSRI) and imipramine (TCA) both acutely (24 hours) and chronically (15 days). Only the chronic treatment showed an up-regulation of miR-1202 expression levels, followed by a reduction of GRM4 mRNA (Lopez et al. 2014).
Furthermore, Lopez and colleagues investigated the regulation of miR-1202 in relation with citalopram treatment. Interestingly, patients who responded to the treatment showed, at baseline, lower miR-1202 plasma levels as compared to both controls and non-responders, whereas after 8 weeks of treatment the miR-1202 expression levels in responders reached a peak, exceeding the levels observed in controls (Lopez et al. 2014), suggesting a possible role of miR-1202 as a biomarker for antidepressant response. Moreover, a similar trend for decreased levels of miR-1202 at baseline was observed also in two other independent cohorts of depressed patients who responded to 8-weeks with escitalopram (SSRI) and desvelfaxine, (SNRI) treatment (Fiori et al. 2017). Indeed, in line with the results of Lopez and colleagues, 8 weeks of antidepressant treatment increased miR-1202 expression levels compared to baseline also in these cohorts (Fiori et al. 2017). Moreover, this study suggests that miR-1202 levels predict the non-responsiveness to antidepressant treatment with a sensitivity of 91,7% and a specificity of 57,7% (Fiori et al., 2017).

MiR-16 has been widely involved in the pathophysiology of depression; for examples, Baudry and colleagues demonstrated that the serotonin transporter (SERT) expression, a well-known vulnerability gene for depression, is modulated by miR-16 in 1C11 neuroectodermal cell line (Baudry et al. 2010). In particular, in these cells the over-expression of miR-16 resulted in a decrease of SERT protein levels as the inhibition of the miRNA unlocks the SERT protein expression. Accordingly, the work of Song and collaborators showed a down-regulation of miR-16 expression levels in CSF of drug-free depressed patients compared to controls as well as reduced CSF serotonin levels, since the down-regulation of miR-16 produces an up-regulation of SERT and the subsequent increase of serotonin re-uptake (Song et al. 2015). Given these findings, researches tried to visualise a possible application of miR-16 as a biomarker for antidepressant drug effect. For example, Li and colleagues showed increased miR-16 levels in depressed patients after 4 weeks of SSRI treatment compared to baseline. However, no changes in miR-16 levels were found in the group of patients treated with SNRI, suggesting that different antidepressant drugs might differently affect specific sets of miRNAs (Lin et al. 2018).
Interestingly, the serotonin transporter and the serotonin receptor-1a transcripts are also targeted by miR-135. Issler and colleagues showed increased blood miR-135 levels in depressed subjects undergoing cognitive behavioural therapy (CBT), but not in depressed patients treated with escitalopram for 12-weeks, suggesting that miR-135a in human blood might be a possible biomarkers for the antidepressant drug effect but larger cohorts are required to investigate its possible clinical involvement (Issler et al. 2014).
MiR-124 regulates growth, proliferation and apoptosis in the central nervous system (Cheng et al. 2009) and a significantly higher expression of miR-124 in PBMCs has been reported in depressed patients, at baseline before escitalopram treatment, and the levels sharply decreased after 8 weeks of therapy, especially in responders, suggesting a role of this miRNA as modulator of treatment effect (He et al. 2016). These results have been also validated in other cohorts where He and colleagues showed that miR-124 levels were reduced

after 4 weeks of treatment with the traditional Chinese antidepressant medicine Chaihu-Shigau-San and that this miRNA decrease paralleled an upregulation of the mRNA and protein levels of the miR-124 predicted target genes mitogen-activated protein kinase 14 (MAPK14) and glutamate receptor subunit 3 (Gria3) (Liu et al. 2018).

5.2 Animal Models

In order to identify and discuss papers describing miRNAs modulated by antidepressant drugs and that might be potential biomarkers for antidepressant response, we searched in Pubmed using the following keywords: "animal models", "rats", "mouse" "miRNAs", "antidepressants", "antidepressant response" and "biomarkers" and we considered only studies describing the role of miRNAs in the mechanisms underlying the effects of antidepressant drugs. We found 15 relevant studies (Table 5) and in the present paragraph we have decided to describe the effect of pharmacological treatment on miR-16 and miR-124, as they have been investigated in at least two studies.

Among the plethora of miRNAs related to antidepressant treatment, miR-16 has been suggested to be a promising miRNA able to mediate the effect on hippocampal neurogenesis induced by SSRI treatment (Launay et al. 2011). Interestingly, Launay and colleagues showed that a three-days stereotaxic injection in the raphe with the SSRI fluoxetine down-regulated miR-16 in mice hippocampus, an effect which also correlated with an increase in SERT expression. Conversely, the direct injection of anti-miR-16 in the hippocampus increased the levels of SERT, similarly to fluoxetine injection in the raphe. These findings suggest that the fluoxetine-mediated down-regulation of miR-16 in the hippocampus has an antidepressant activity (Launay et al. 2011). However, the data are in contrast with the results of the study on human cohorts, previously described (Song et al. 2015; Li et al. 2018). A rigorous attention to miR-16 activity has been paid also by Baudry and colleagues (2010) as they showed an increase in miR-16 expression levels in the raphe of mice which were infused with fluoxetine for 3 days. The fluoxetine-induced upregulation of this miRNA is probably due to the activity of a pre/pri-miRNA-16, whose levels are inversely correlated to those of the mature miRNA (Baudry et al. 2010). On the other hand, a twenty-days infusion of fluoxetine reduced miR-16 expression both in mice hippocampus and raphe (Baudry et al. 2010; Launay et al. 2011).

In the study of Pan and Liu, miR-124a was shown to be modulated by the administration of the antidepressant drug duloxetine. Adult mice were exposed to a set of chronic unpredictable mild stressors for 4 weeks and then received the SNRI drug for 3 weeks. The authors observed an up-regulation of miR-124a and miR-134 in the hippocampus of mice exposed to the stress paradigm, whereas miR-132 and miR-18 were down-regulated. After the administration of duloxetine, the elevated levels of both miR-124a and miR-134 significantly dropped, suggesting that the modulation of these levels was directly mediated by the SNRI drug (Pan and Liu 2015). The modulation of miR-124a by antidepressant drugs was investigated also by Higuchi and colleagues in a group of mice exposed to chronic ultra-mild stress. The animals were exposed to the stressful paradigm for 6 weeks and were administered the tricyclic antidepressant drug imipramine for the last 3 weeks of the paradigm. The levels of pre/pri mir-124a and the mature miR-124a were downregulated in the hippocampus of stressed mice and this effect was blocked by the administration

of imipramine, both for pre/pri and the mature miR-124a, suggesting that the modulation of miR-124a is mediated by imipramine (Higuchi et al. 2016).

miRNAs	*Samples/Tissue*	*Antidepressant Drug*	*Results*	*References*
miR-134		ginsenoside Rg1	ginsenoside Rg1 may exhibit neuroprotection and antidepressant-like effects by activating the CREB-BDNF system within the BLA in this rat model of depression.	*Yu et al. 2018*
miR-16, miR-30, miR-34, miR-128, miR-132, miR-134, miR-182, miR-183, miR-185, miR-212	Serum	Different SSRI and SNRI	In patients treated with SSRI, miR-16 levels increased significantly after treatment. Therefore, miR-183 and miR-212 levels increased significantly after four weeks of antidepressant treatment.	*Lin et al. 2018*
miR-451a *miR-34a-5p* *miR-221-3P*	Serum	Paroxetine	Depressed patients had lower serum miRNA-451a but higher serum miRNA-34a-5p and miRNA-221-3p, and these miRNAs are potential predictors of the efficacy of antidepressants.	*Kuang et al. 2018*
miR-151a-3p *miR-221/222*	Lymphoblastoid cell lines	SSRI (paroxetine)	miR-151a-3p, miR-221/222 and their (here confirmed) respective target-genes, CHL1 and ITGB3, are implicated in SSRI responsiveness, and possibly in the clinical response to antidepressant drugs.	*Oved et al. 2017*
miR-130b *miR-26a/26b* *let-7f* *miR-770-5p* *miR-34c-5p*	Human U87 glioblastoma cells	Escitalopram	Significant increase of let-7f, both after 48h and 72h (p=0.022) of treatment and of miR-26a after 48h.	*Maffioletti et al. 2017*
miR-146a-5p *miR-146b-5p* *miR-425-3p* *miR-24-3p*	Blood	Duloxetine	Our results revealed differential expression of miR-146a-5p, miR-146b-5p, miR-425-3p and miR-24-3p according to treatment response. These miRNAs are consistent markers of treatment response and regulators of MAPK/Wnt systems.	*Lopez et al. 2017*

miR-1202 *miR-135a* *miR-16*	Blood	Escitalopram or Desvenlafaxine or Duloxetine	In two different cohorts, responders displayed lower baseline miR-1202 levels compared with non-responders, which increased following treatment.	*Fiori et al. 2017*
miR-1202	Blood	Desvenlafaxine	Changes in peripheral miR-1202 levels were therefore associated with changes in brain activity and connectivity in a network of brain regions associated with depression and antidepressant response.	*Lopez et al. 2017*
miR-572 *miR-663a*	Neuroblastoma cell lines	Fluoxetine	Fluoxetine could increase the expression of miRNAs in undifferentiated neural cells, and that putative target genes of those miRNAs have been shown to be involved in fundamental neurodevelopmental processes.	*Mundalil Vasu et al. 2016*
414 miRNAs	Blood	Citalopram	414 miRNAs may regulate one or several modules associated with clinical improvement. By contrast, only 12 miRNAs were predicted to specifically regulate modules unrelated to clinical improvement.	*Belzeaux et al. 2016*
Several miRNAs	Blood	Escitalopram	40 different miRNAs were differently expressed after treatment; twenty-three significantly overexpressed and 17 down-regulated.	*Enatescu et al. 2016*
miR-124	PBMC	Different antidepressant drugs	The expression levels of miR-124 from PBMCs in MDD patients were significantly higher than those in healthy controls. In addition, the expression levels of miR-124 were significantly down-regulated after eight weeks of treatment.	*He et al. 2016*
miR-355	Blood	Citalopram	Antidepressant drug treatment with citalopram can upregulate miR-335 expression and downregulate GRM4 expression.	*Li et al. 2015*

miR-135	Blood	Escitalopram	Trend for higher expression after CBT vs escitalopram	*Issler et al. 2014*
miR-1202	Human Neural Progenitor cells (NPCs) and Whole Blood	Citalopram or Imipramine	miR-1202 is associated with the pathophysiology of depression and is a potential target for new antidepressant treatments.	*Lopez et al. 2014*
miR-221 *miR-222*	Human Lymphoblastoid ccell lines	Paroxetine	Decreased expression of miR-221 and miR-222 after paroxetina treatment, both predicted to target ITGB3.	*Oved et al. 2013*
30 miRNAs	Blood	Escitalopram	Thirty miRNAs were differentially expressed after the AD treatment: 28 miRNAs were up-regulated, and 2 miRNAs were strongly down-regulated	*Bocchio-Chiavetto et al. 2013*
miR-151-3p *miR-212* *miR-132* *miR-30b** *let-7b* *let-7c*	Human Lymphoblastoid ccell lines	Paroxetine	These miRNAs has a potential values as SSRI response biomarkers.	*Oved et al. 2012*
miR-145 *miR-20b*	PBMC	Personalized antidepressant	Both miRNAs increase in expression level during treatment in responders.	*Belzeaux et al. 2012*

Table 4. Summary of miRNAs modulated by antidepressant drugs in human samples.

miRNAs	*Samples/Tissue*	*Antidepressant Drug*	*Results*	*References*
64 miRNAs	Hippocampus (mice)	Paroxetine	64 miRNAs showed significant changes between fluoxetine treatment and control groups by analyzing 626 mouse miRNAs.	*Miao et al. 2018*
miR-448-3p *miR-764-5p* *miR-1264-3p* *miR-1298-5p* *miR-1912-3p*	Hippocampus (mice)	Ketamine	Administration of an antagonist to miRNA 448-3p diminished the antidepressant effect of ketamine in the learned helplessness paradigm, indicating that up-regulation of miRNA 448-3p provides an antidepressant action.	*Grieco et al. 2017*
miR-124	Hippocampus (mice)	Imipramine	Mouse exposed to chronic unpredictable mild stress expressed reduced miR-124 levels in hippocampus. This effect is reverted by imipramine.	*Higuchi et al. 2016*
miR-132 *miR-18a* *miR-134* *miR-124a*	Frontal lobe and hippocampus (mice)	Duloxetine	A significant upregulation of miR-132 and miR-18a in hippocampus in the duloxetine treatment group compared with model group, whereas the levels of miR-134 and miR-124a were significantly downregulated. miR-18a showed significant upregulation in frontal lobe in the duloxetine treatment group relative to model group.	*Pan and Liu 2015*
miR-9 *miR-326*	Brain tissue (rat)	Escitalopram	Early life stress enhanced the susceptibility to late life stress and resistance to escitalopram treatment through decreasing microRNA-9 expression and subsequently upregulating dopamine receptor D2 expression in the nucleus accumbens. microRNA-326 may be a novel target of escitalopram.	*Zhang et al. 2015*

miR-135		Imipramine or Fluoxetine	Chronic treatment with imipramine or fluoxetine (but not with reboxetine) is able to up-regulate miR-135 in a chronic social defeat mice, a well-established model of depression.	*Issler et al. 2014*
miR-132	Hippocampus (male mice)	Oleanolic acid	The oleanolic acid induces the upregulation of miR-132, activating of the hippocampal BDNF-ERK-CREB signalling pathways	*Yi et al. 2014*
15 common miRNAs	Hippocampus (mice)	7-Chlorokynurenic acid (7-CTKA)	The 15 miRNA targets shared by TrkB-ERK/Akt pathways might participate in rapid-acting molecular mechanism of antidepressant 7-CTKA	*Liu et al. 2014*
miR-206	Hippocampus (rat)	Ketamine	miR-206 is involved in novel therapeutic targets for the anti-depressive effect of ketamine	*Yang et al. 2014*
miR-125 miR-182	Hippocampus (rat)	Chaihu Shugan San	miR-125a and miR-182 recover to normal after intervention with Chaihu Shugan San, which may be the target points of its antidepressant effect.	*Cao et al. 2013*
miR-1971	Prefrontal cortices (PFCs)	Fluoxetine	The therapeutic action of fluoxetine in shocked mice is associated with a significant reduction in mmu-miR-1971 expression	*Schmidt et al. 2013*
miR-212	Dentate girus (rat) and Blood	Electroconvulsive stimulation (ECS)	miRNA miR-212 were significantly increased in rat dentate gyrus following both acute and chronic ECS. MiR-212 levels also increased in whole blood following chronic ECS.	*Ryan et al. 2013*
miR-598-5p	Hippocampus (rat)	Electroconvulsive Shock Therapy and Ketamine	Electroconvulsive shock therapy and Ketamine possessed miR-598-5p as a common target.	*O'Connor et al. 2013*

miR-16	Hippocampus (mouse)	Fluoxetine	Fluoxetine, acting on serotonergic raphe neurons, decreases the amount of miR-16 in the hippocampus, which in turn increases the levels of the serotonin transporter (SERT).	*Launay et al. 2011*
miR-16	Raphe Nuclei (mouse)	Fluoxetine	In mice, chronic treatment with the SSRI fluoxetine (Prozac) increases miR-16 levels in serotonergic raphe nuclei, which reduces SERT expression	*Baudry et al. 2010*

Table 5. Summary of miRNAs modulated by antidepressant drugs in animal models.

6. miRNA-based therapeutics

RNA interference (RNAi) is a regulatory mechanism based on the use of small double-stranded RNA (dsRNA) molecules as triggers to direct homology-dependent control of gene activity (Almeida et al. 2005). The RNAi can be artificially induced by introducing a small double-stranded fragment of RNA, which corresponds to a particular mRNA into a cell. The RISC complex within the cell recognizes this double-stranded RNA fragment and uses the guide strand to bind and destroy its corresponding cellular mRNA target, blocking the translation of the encoded protein. Indeed, as the dysregulation of miRNA expression and the subsequent absence of mRNA regulation could lead to a general deregulation of tissue-specific gene expression, contributing to the development of diseases, the modulation of miRNA expression might be an innovative therapeutic tool, as the artificial RNAi could potentially block the translation of specific proteins, which play a pathological role in the development of psychiatric diseases (Castanotto and Rossi 2009).

Similarly, transfection of miRNAs mimics represents another technique that is increasingly being used to over-express a specific miRNA and, therefore, to examine its biological effects on cell function. Generally, the mimic, which contains the same sequences of the endogenous miRNA of interest, can increase its expression levels (Matsukura et al., 2016), allowing to reveal the effects of the miRNA over-expression on biological functions.

However, to date, several drawbacks and challenges of both miRNAs silencing and gain-of-function experiments in the research of psychiatric disorders are still unsolved.

The first RNA-based therapeutic strategies had very low bioavailability due to the potential degradation of the oligonucleotides by RNase in serum or in endocytic compartment of cells (Rupaimoole and Slack. 2017). Moreover, the difficulties of reaching the target site by RNA-drugs are noteworthy due to the difficulties to targeting the oligodendrocytes to specific tissue and body fluids. Due to all these issues, the initial studies were mostly unsuccessful and the need to improve the methodology resulted urgent and necessary. In order to bypass obstacles related to the bioavailability, the oligonucleotides underwent different strategies: i) modifying the chemistry of oligodendrocytes by altering the nucleotides backbone or adding phosphonothioate groups; ii) developing delivery systems able to circumscribe miRNAs. The former approach has been the most widespread, whereas, recently, more efforts have been made in order to develop non-toxic and safe delivery systems.

To date, no miRNA-based therapeutics have been approved by FDA (Food and Drug Administration) or EMA (European Medicines Agency) and the majority are still in the preclinical phase or are entering clinical trials. The therapeutic miRNAs that are in the developmental phase are engineered to treat mainly cancers and hepatitis C virus related disorders, as well as cardiovascular diseases (Chakraborty et al. 2017). Unfortunately, no miRNA-based therapeutics for the treatment of psychiatric disease have reached the pre-clinical stage during the past years, showing the urgent need to increase the efforts of identifying clear miRNAs targeting molecules known to be involved in the pathogenesis or development of psychiatric disease.

7. Conclusions

According to the World Health Association, depression in the first invalidated disease worldwide and the burden of depression is increasing year by year. Beside the well-known biological causes of depression, such as the depletion of monoamines and the neurotrophic hypothesis, stress is another cause deeply involved in the onset of depression, due to the deregulation of the HPA axis. Nowadays, stress is inevitably part of our everyday life and, during the lifespan, we are likely experiencing stressful events from childhood to later in life. However, whether several people worldwide might come across traumas during childhood or adolescence or adulthood, fortunately not all develop psychiatric diseases such as depression. For this reason, during the last decades researchers have focused their attention on the identification of stress copying mechanisms able to explain the resilience or vulnerability of developing psychiatric diseases. In this context, researchers have paid close attention on several genetic and epigenetic mechanisms involved in the dysregulation of the brain homeostasis; among the plethora of biological mechanisms which could be involved, epigenetic modifications, especially miRNAs, have drawn the attention of the scientists. MiRNAs are involved in the onset of depression as well as in the vulnerability and/or resilience to stressful events and the subsequent onset of depression. Both animal and human studies have shown that some miRNAs might be considered as biomarkers due to their different expression after stress exposure and predicting the onset of psychiatric conditions. For this reason, the evaluation of miRNAs expression in peripheral blood or tissues might be a breakthrough in the diagnosis and prevention of depression.

Moreover, the burden of depression is exacerbated by the lack of efficacy of antidepressant drugs, given that about 30% of depressed patients do not respond to the first-line antidepressant therapy. As a consequence, both new antidepressant drugs and pharmacological targets are extremely needed to improve the antidepressant therapy. A few studies have implied miRNAs as therapeutic tools to regulate the expression of genes involved in the pathogenesis of diseases; however, no miRNAs for depression or psychiatric diseases have been approved by Authorities (FDA or EMA) or even enter into clinical trials. Therefore, further studies are strongly required to find new antidepressant targets and to employ miRNAs in the clinical settings.

In conclusion, given that miRNAs are involved in the pathogenesis of depression and in stress resilience and vulnerability, they might be implied also in predicting the antidepressant response or might be used as proper antidepressant drugs.

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