MiR in Major Depressive Disorder

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Major depressive disorder (MDD) is a complex neuropsychiatric disorder with an increasing incidence and a 2–20% prevalence in the worldwide general population, being the leading cause of disability around the world. A significant decrease in life quality, functional impairment, and other psychosocial aspects, as well as comorbidities are associated with MDD, among others.

Keywords: major depressive disorder ; microRNAs ; biomarkers ; antidepressant treatment

1. Introduction

Major depressive disorder (MDD) is a complex neuropsychiatric disorder with an increasing incidence and a 2–20% prevalence in the worldwide general population [1], being the leading cause of disability around the world [2]. A significant decrease in life quality, functional impairment, and other psychosocial aspects, as well as comorbidities are associated with MDD, among others. What is more, a high degree of disability, morbidity, and mortality by suicide (suicidal ideation) causes MDD to be considered a major public health concern in developed countries [3].

Although tremendous efforts have been made in order to better understand and characterize this debilitating illness, current knowledge regarding MDD pathophysiology and neurobiology have failed to completely elucidate its molecular particularities to a greater extent. As a consequence, about 40% of patients with MDD do not respond to antidepressant treatment (AD) and eventually become treatment-resistant as the disease burden increases [4]. In addition, although being diagnosed at relatively early ages in a somewhat efficient fashion, the lack of uniform and accurate diagnostic tools (biomarkers) may lead to difficulties in assessing the differences between MDD and other etiologically related diseases, such as bipolar disorder (BD) [5]. Performing the Diagnosis and Statistical Manual of Mental Disorders (DSM-5) and the 11th Revision of the International Classification of Diseases (ICD 11) as the gold standard diagnostic criterion applied to patients was shown to induce interviewer bias, especially if performed by only one health specialist, which might lead to misdiagnosis in many cases [6]. Moderate reliability has been attributed to the Structured Clinical Interview for DSM-IV Axis I Disorders as well (SCID-I) [7][8][9].

To date, it is known that MDD patients suffer multiple alterations in different regions of the brain, compared to healthy subjects. Studies have shown that qualitatively, synaptic circuits and neural, functional, and structural plasticity are steadily impaired, while connectivity between different brain regions is disrupted. The latter affects communication between subcortical areas involved in modulating negative emotions, the frontal lobe with other brain regions, ultimately affecting cognition, memory, and learning [10][11][12]. Evidence reveals that MDD subjects present a smaller hippocampal volume, a modified morphology (number and shape) of dendrites, and the atrophy of neurons [13][14][15][16][17][18].

2. Research Articles

All research articles included in this study were retrieved by interrogating the PubMed, Web of Knowledge, and DirectScience databases (up to 20 of March 2021) with the following combination of key words: (“depression” or “depressive disorder”), and (“microRNA” or “miR”), and (“blood compartments”), and (“diagnosis”), and (“treatment” or “antidepressant treatment” or “antidepressant” or “therapy”), and (“biomarker”). The references from the articles of interest were analyzed to identify other relevant reports.

Research articles’ inclusion criteria were: (1) case-control studies in human subjects on depression assessing miRs’ expression level, with or without AD, (2) studies evaluating the diagnostic potential of different miRs in MDD, (3) MDD diagnosed based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), (4) a control group consisting of healthy subjects, and (5) published in the English language.

Research articles' exclusion criteria were: (1) studies not conducted on human subjects, (2) studies assessing miR expression in body fluids other than blood, (3) nonoriginal papers, such as conference abstracts, letters to editors, and reviews, (4) duplicate studies, and (5) papers not written in the English language.

Researchers further considered for analysis only research articles that presented data related to the screening and validation of miRs in MDD from blood compartments (whole blood, serum, total plasma (TP) , plasma exosomes, exosome-depleted plasma (EDP), and peripheral blood mononuclear cells (PBMCs)). Extracellular vesicle (EV)-entrapped miRs, such as in exosomes, have also been explored as sources of biomarkers for MDD.

3. Current Studies

Table 1 presents for each study the sample size (number of cases/controls), the blood compartment used for the analyses (some authors did not specify this), and miR findings and expression (upregulated, downregulated, or unchanged miRs) in depressive patients compared to healthy controls.

Table 1. miRs' expression in different blood compartments of patients with MDD compared to healthy controls.

Study (Year, Reference No)	Patients	Controls	Blood Compartment	Upregulated miRs	Downregulated miRs	Unchanged miRs	Total
Belzeaux et al., 2012 [19]	16	13	PBMCs	miR-107 miR-133a miR-148a miR-425-3p miR-494 miR-579 miR-652 miR-941 miR-589	miR-200c miR-381 miR-571 miR-636 miR-1243	-	9 upregulated, 5 downregulated
Li YJ et al., 2013 [20]	40	40	Serum	miR-132 miR-182	-	-	2 upregulated
Fan et al., 2014 [21]	81	46	PBMCs	miR-26b miR-1972 miR-4485 miR-4498 miR-4743	-	-	5 upregulated
Li J et al., 2015 [22]	18	18	Whole blood	miR-644 miR-450b miR-328 miR-182	miR-335 miR-583 miR-708a miR-650 miR-654a	miR-541 miR-663 miR-578	4 upregulated, 5 downregulated, 3 unchanged
Camkurt et al., 2015 [23]	50	41	Plasma	miR-451a miR-17-5p miR-223-3p	miR-320a	miR-25-3p miR-126-3p miR-16-5p miR-93-5p	3 upregulated, 1 downregulated, 4 unchanged
Wan et al., 2015 [24]	38	27	Serum	let-7d-3p miR-34a-5p miR-221-3p miR-125a-5p miR-30a-5p miR-29b-3p miR-10a-5p miR-375 miR-155–5p miR-33a-5p miR-139–5p	miR-451a miR-15b-5p miR-106-5p miR-590-5p miR-185-5p	-	11 upregulated, 5 downregulated
Wang X et al., 2015 [25]	169	52	Plasma	-	miR-144-5p	-	1 downregulated

Study (Year, Reference No)	Patients	Controls	Blood Compartment	Upregulated miRs	Downregulated miRs	Unchanged miRs	Total
Mafioletti et al., 2016 [26]	20	20	Peripheral venous blood	hsa-miR-199a-5p hsa-miR-24-3p hsa-miR-425-3p hsa-miR-29c-5p hsa-miR-330-3p hsamiR-345-5p	hsa-let-7a-5p hsa-let-7d-5p has-let-7f-5p has-miR-1915-3p	hsa-miR-720 hsa-miR-140-3p hsa-miR-1973 hsa-miR-30d-5p hsa-miR-3158-3p hsa-miR-330-5p hsa-miR-378a-5p hsa-miR-1915-5p hsa-miR-1972 hsa-miR-21-3p hsa-miR-4521 hsa-miR-4793-3p hsa-miR-4440	6 upregulated, 4 downregulated, 13 unchanged
Sun et al., 2016 [27]	32	32	Peripheral blood leukocytes	miR-34b-5p miR-34c-5p	-	miR-369–3p miR-381 miR-107	2 upregulated, 3 unchanged
He et al., 2016 [28]	32	30	PBMCs	miR-124	-	-	1 upregulated
Roy et al., 2017 [29]	18	17	Serum	miR-124-3p	-	-	1 upregulated
Kuang et al., 2018 [30]	84	78	Serum	miR-34a-5p miR-221-3p	miR-451a	-	2 upregulated, 1 downregulated
Fang Y et al., 2018 [31]	45	32	Plasma	miR-124 miR-132	-	-	2 upregulated
Gheysarzadeh et al., 2018 [32]	39	36	Serum	-	miR-16 miR-135a miR-1202	-	3 downregulated
Hung et al., 2019 [33]	84	43	PBMCs	miR-21-5p miR-145 miR-223	miR-146a miR-155 let-7e	-	3 upregulated, 3 downregulated

Table 2 shows the sample characteristics for each study investigating miRs before and after AD in MDD patients, the blood compartment used for the analyses, and miR findings and expression level changes in depressive patients, before and after AD.

Table 2. miR changes in expression levels before and after antidepressant (AD) treatment.

Study	Patients	AD Treatment and Duration	Blood Compartment	Upregulated miRs	Downregulated miR	Unchanged miRs	Total
Enatescu et al., 2016 [34]	5	Escitalopram 12 weeks	Plasma	miR-1193 miR-3173-3p miR-3154 miR-129-5p miR-3661 miR-1287 miR-532-3p miR-2278 miR-3150a-3p miR-3909 miR-937 miR-676 miR-489 miR-637 miR-608 miR-4263 miR-382 miR-3691-5p miR-375 miR-433 miR-1298 miR-1909 miR-1471	miR-99b miR-151-5p miR-223 miR-181b miR-26a miR-744 miR-301b miR-27a miR-24 miR-146a- miR-146b-5p miR-126 miR-151-3p let-7d miR-221 miR-125a-5p miR-652	-	23 upregulated, 17 downregulated
Li J et al., 2015 [22]	18	Citalopram, 1 week	Whole blood	miR-335	-	-	1 upregulated
Wang X et al., 2015 [25]	169	Not mentioned, 8 weeks	Plasma	miR-144-5p miR-30a-5p	-	-	2 upregulated
He et al., 2016 [28]	32	Venlafaxine (*N* = 7), paroxetine (*N* = 7), fluoxetine (*N* = 3), escitalopram (*N* = 11), duloxetine (N = 1), sertraline (*N* = 3), mirtazapine (*N* = 2)	PBMCs	-	miR-124	-	1 downregulated
Kuang et al., 2018 [30]	84	Paroxetine 8 weeks	Serum	miR-34a-5p miR-221a-3p	miR-451a	-	2 upregulated, 1 downregulated
Fang Y et al., 2018 [31]	32	Citalopram 8 weeks	Plasma	miR-124	miR-132	-	1 upregulated, 1 downregulated
Hung YY et al., 2019 [33]	84	Not mentioned, 4 weeks	PBMCs	miR-146a miR-155 let-7e	-	-	3 upregulated

Study	Patients	AD Treatment and Duration	Blood Compartment	Upregulated miRs	Downregulated miR	Unchanged miRs	Total
Bocchio-Chiavetto et al., 2013 [35]	10	Escitalopram 10 weeks	Whole blood	miR-130b miR-505 miR-29b-2 miR-26b miR-22 miR-26a miR-64 miR-494 let-7d let-7g let-7e let-7f miR-629 miR-106b miR-103 miR-191 miR-128 miR-502-3p miR-374b miR-132 miR-30d miR-500 miR-589 miR-183 miR-574-3p miR-140-3p miR-335 miR-361-5p	miR-34c-5p miR-770-5p	-	26 upregulated, 2 downregulated
Zhang et al., 2014 [36]	20	Venlafaxine, sertraline, mirtazapine 6 weeks	PBMCs	-	miR-1972 miR-4485 miR-4498 miR-4743	miR-26b	4 upregulated, 1 downregulated
Lopez et al., 2017 [37]	23	Escitalopram 8 weeks	Peripheral blood	miR-1202	-	-	1 upregulated
Lin CC et al., 2018 [38]	33	Not mentioned, 4 weeks	Whole blood	miR-16 miR-183 miR-212	-	-	3 upregulated

Interestingly, the majority of miRs studies changed their expression pattern after AD treatment, but some maintained their expression level. This is the case of miR-494, -589, -26b, -34a-5p, -124, and -132, which remained upregulated even after treatment, while miR-451a remained downregulated after treatment.

4. Discussion

Mounting evidence suggests that a tremendous number of miR species possess a dysregulated expression pattern in MDD patients relative to healthy controls. miR-132 was among the top-ranked upregulated miRs within the studies, with evidence demonstrating its direct involvement in the pathophysiology of MDD. Animal studies have shown that the increase in miR-132 expression negatively correlated with brain-derived neurotrophic factor (BDNF) expression and that inhibiting miR-132 leads to an increase in BDNF expression and to the reduction of depression symptoms. Moreover, a high miR-132 expression level leads to short-term memory and learning impairment [20].

In addition, some miRs kept their expression levels constant even after administration of AD treatment (let-7e, miR-183, and miR-335); however, contradictory studies exist, and their exact role in MDD etiopathogenesis is yet to be understood [39][40].

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