MicroRNAs, Multiple Sclerosis, and Depression

Subjects: Medicine, Research & Experimental
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Multiple sclerosis (MS) is a chronic disease of the central nervous system that affects the brain and spinal cord. There are several disease courses in MS including relapsing–remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). Up to 50% of MS patients experience depressive disorders. Major depression (MD) is a serious comorbidity of MS. Many dysfunctions including neuroinflammation, peripheral inflammation, gut dysbiosis, chronic oxidative and nitrosative stress, and neuroendocrine and mitochondrial abnormalities may contribute to the comorbidity between MS and MD. In addition to these actions, medical treatment and microRNA (miRNA) regulation may also be involved in the mechanisms of the comorbidity between MS and MD.

Keywords: biomarker ; depression ; microRNA ; multiple sclerosis

1. MicroRNA

miRNA is a small non-coding RNA with a length of about 21–24 nucleotides. It has important functions in cell differentiation, development, cell cycle regulation, and apoptosis. miRNAs can regulate up to 30% of the protein-coding genes in the human genome [1], and it is well known that they are involved in the development of many diseases. Strong evidence revealed that in cancer cells, miRNAs were dysregulated due to various mechanisms including abnormal transcriptional controls of miRNAs, dysregulated epigenetic changes, and defects in the miRNA biogenesis pathway [2]. As a result, miRNAs are good biological biomarkers of various cancers, and many bioinformatics tools have been developed to predict miRNA biomarkers of cancers [3][4][5][6][7][8].

One of the main barriers to cancer chemotherapy is the drug resistance problem. miRNAs were also shown to contribute to the development of resistance against chemotherapy [9]. In addition to cancers, abnormal miRNA expression also contributes to neurological and psychiatric diseases such as frontotemporal dementia, Alzheimer's disease, Parkinson's disease, spinal muscular atrophy, amyotrophic lateral sclerosis, and anti-NMDA receptor encephalitis [10][11][12][13][14][15]. miRNA biomarkers have been used to explore the association between different diseases and the association between vaccination and diseases [15][16][17].

2. MicroRNA Biomarkers

Many common miRNA biomarkers of both diseases are presented in **Table 1**. Nevertheless, there may be more common miRNA biomarkers of MS and MD than those listed in **Table 1**.

Table 1. The common miRNA biomarkers of MS and MD are provided. The expression information with parentheses means the expression information after the treatment of the drug.

miRNA	MS miRNA Expression	MS References	MD miRNA Expression	MD References
miR-125a	↑, ↓**(Natalizumab)**	[18][19][20][21][22][23][24]	↓,↑, ↓**(Escitalopram)**	[25][26][27][28]
miR-146b	↑	[18][29]	↓**(Escitalopram),** ↑**(Duloxetine)**	[25] [30]
miR-200c	↑	[18][29]	↓	[31]
miR-328	↓,↑	[18][24][29][32]	↑	[28][33]
miR-199a	↑,↓	[18][29][32][34][35]	↑	[28][36]
miR-152	↓,↑	[18]	↑**(Lithium)**	[37]
miR-650	↑	[29][38]	↓	[28][31]

miRNA	MS miRNA Expression	MS References	MD miRNA Expression	MD References
miR-326	↑, ↓(Natalizumab)	[19][29][39][40][41]	↓	[42]
miR-142	↑,↓	[29][35][43]	↓,↑	[44][45]
miR-21	↑,↓	[29][46]	↓	[47]
miR-27a	↑	[22][29][48]	↓	[25][44][49]
miR-193a	↑	[29][50]	↓	[51]
miR-15a	↑	[29][52]	↑	[53]
miR-130a	↑	[29]	↓	[44]
miR-22	↑	[29][43]	↓,↑(Escitalopram)	[49][51][54]
miR-320	↑	[20][29][55]	↓	[28][56]
miR-214	↑,↓	[29][48]	↑	[57]
miR-184	↓	[22][29][58]	↓,↑	[27][59][60]
miR-139	↓	[29][38]	↑	[28][61][62][63]
miR-23b	↓	[29][64]	↑	[45]
miR-487b	↓	[29][38]	↑	[26][31]
miR-181c	↓	[29][65][66]	↓,↑	[27][31][60]
miR-340	↓,↑	[29][67][68]	↓	[69]
miR-629	↑	[29][70]	↑,↑(Escitalopram)	[49][51][54]
miR-148a	↑	[29][67]	↑	[49][71]
miR-28	↑	[29]		[49]
miR-195	↑	[29]	↑	[63]
miR-497	↑,↓	[29][50][70]	↓	[44]
miR-135a	↑	[29][38][72]	↓	[31][69]
miR-204	↑	[29][38][72]	↑	[73]
miR-660	↑,↓	[29][38][43][72]	↓	[44]
miR-30a	↑,↓	[22][24][29][32][38][70][72]	↑	[28][74]
miR-365	↑,↓	[29][32]	↑	[31]
miR-532	↑,↓	[29][75]	↓,↑(Escitalopram)	[25][28][76]
miR-126	↑	[29][50][77]	↓,↓(Escitalopram)	[25][26][49]
Let-7c	↑, ↓(natalizumab)	[23][29][38][72]	↓	[78]
miR-20b	↑,↓	[24][29][40]	↓	[44]
miR-30d	↑	[29][79]	↑,↑(Escitalopram)	[54][80]
miR-9	↑	[22][29][81]	↓	[26]
miR-219	↓	[22][29]	↓	[82]
miR-338	↓	[22][29]	↑	[76]
miR-642	↓, ↑(natalizumab)	[23][29]	↑	[44]
miR-181b	↓	[29][83]	↓(Escitalopram)	[25]
miR-18a	↓	[29][40]	↑,↑(Duloxetine)	[27][60][84]

miRNA	MS miRNA Expression	MS References	MD miRNA Expression	MD References
miR-190	↓	[29][38]	↓	[44]
miR-213	↓	[29][38]	↑	[85]
miR-330	↓	[29][35]	↑	[28][36]
miR-151	↓	[29][38]	↓**(Escitalopram)**	[25]
miR-140	↓	[29][38]	↑**(Escitalopram)**	[54][60]
miR-146a	↑,↓	[21][22][24][29][32][43][86]	↓, ↑**(Duloxetine),** ↓**(Escitalopram)**	[25][30][31][44]
miR-223	↑,↓	[21][22][29][87]	↑,↓**(Escitalopram)**	[25][28]
miR-30c	↑	[21][34]	↓	[26][88]
miR-155	↑,↓	[21][22][29]	↑,↓,↑**(Lithium)**	[28][31][37][44][49]
miR-124	↓	[21][22]	↑,↓,↓**(Duloxetine)**	[31][76][84][89][90][91]
miR-34a	↑,↓	[22][29][34][50]	↑,↑**(Lithium)**	[28][37][92]
miR-19a	↑,↓	[34][43]	↑	[93]
miR-21	↑,↓	[32][86]	↑,↓	[47][51]
miR-22	↑	[43][94]	↓,↑**(Escitalopram)**	[51][54]
miR-486	↓	[43][50]	↓	[76]
miR-451a	↓,↑	[43][87]	↑	[28][56]
let-7b	↓,↑	[24][43][95]	↓	[78]
miR-320b	↓	[43][96]	↓	[51]
miR-122	↓,↑	[38][43][72]	↓	[51]
miR-215	↓	[43][83]	↑	[97]
miR-26a	↓,↑	[41][43]	↑**(Escitalopram),** ↓**(Escitalopram)**	[25][54]
miR-15b	↓	[43][87]	↑,↓	[28][98]
miR-221	↑	[24][83]	↑	[49]

Most of the miRNAs in **Table 1** are reviewed as follows. The miRNA expression was obtained from the peripheral blood mononuclear leukocytes from 10 Chinese MS patients and 10 healthy controls [18]. Then the study was validated independently using real-time polymerase chain reaction (PCR) in the second cohort of 40 MS patients and 40 controls. The levels of miR-125a, miR-146b, and miR-200c were elevated in these MS patients, whereas miR-328, miR-199a, and miR-152 were decreased. The active lesions in the brains of the early stages of MS patients contain many inflammatory cells and macrophages. Moreover, the cerebrospinal fluid (CSF) of MS patients bearing active demyelinating lesions had abnormally high miR-125a-3p levels [19]. Interleukin 17 (IL-17)-producing T helper cells (TH-17 cells) were shown to be implicated with MS [99]. miR-326 was associated with the pathogenesis of MS by regulating TH-17 differentiation [39]. The protein urocortin 1 (Ucn1) is most abundantly expressed in the midbrain, and depressed suicide completers have upregulated midbrain Ucn1 expression levels compared with control individuals [100]. miR-326 acted as a molecular switch in the regulation of midbrain Ucn1 expression [42]. A DNA methylation analysis was performed in CD4+ T cells from RRMS, SPMS, and healthy individuals [46]. RRMS patients had lower levels of miR-21 compared to SPMS patients and healthy individuals. Ahmadian-Elmi et al. compared 40 RRMS patients including 20 samples in relapsing and 20 samples in remitting phases with the control group [48]. miR-27a was upregulated in the relapsing phase compared to the remitting phase and healthy individuals, while miR-214 was downregulated in the relapsing phase compared to remitting phase and healthy individuals. miR-15a was downregulated in CD4+ T cells from RRMS patients [52]. miR-320a and miR-125a-5p were significantly upregulated in pediatric MS and adult-onset MS patients [20]. miR-184 could promote oligodendrocyte differentiation that was involved in developing a cell-based therapy for MS [58]. miR-23b, which could halt the progression of experimental autoimmune encephalomyelitis (EAE), was a potential therapeutic target in the amelioration of MS [64].

Elevated levels of miR-181c were observed in the CSF of MS patients [65]. miR-340 expression in memory CD4+ T-cells increased in MS patients [67][68]. miR-629 was upregulated, but miR-30a-3p and miR-497 were downregulated in CD8+ T cells from peripheral blood samples of RRMS patients [70]. Some differentially expressed miRNAs obtained from several studies were validated in 86 MS patients and 55 controls [32]. miR-328 and miR-30a were upregulated in MS patients, and miR-21, miR-199a, miR-365, and miR-146a were downregulated in MS patients compared with controls. Bioinformatics analysis revealed that miR-532-5p was differentially expressed in RRMS patients, and a digital quantitative PCR method confirmed the downregulation of exosomal miR-532-5p in RRMS relapse patients [75]. Compared with 20 healthy controls, miR-126-5p was upregulated in 17 RRMS patients [77]. Longitudinal analysis revealed that miR-18a and miR-20b were upregulated and predominantly expressed in CD4+ T cells from RRMS patients, whereas miR-326 was downregulated upon natalizumab treatment. An upregulation of miR-9-5p in the relapsing phase of 40 MS patients was observed compared with 11 healthy controls that suggested a possible inducing role of miR-9-5p in the pathway of Th17 cells during MS pathogenesis [81]. MS was characterized by the demyelination of central nervous system neurons. miRNAs play a role in remyelination, contributing to MS, including miR-219, miR-338, miR-125a, miR-27a, miR-146a, miR-9, miR-23, miR-184, miR-124, miR-223, miR-155, miR-30a, miR-34a, miR-326, and miR-27. Compared with the baseline, let-7c and miR-125a-5p were decreased, while miR-642 was increased after 6 and 12 months of the natalizumab therapy [23]. miR-142-5p, miR-199a-5p, and miR-330-3p showed a significant difference between MS patients and controls in terms of the expanded disability status scale score [35]. TaqMan array analysis showed that miR-126, miR-193a, and miR-486 were significantly increased, whereas miR-34a was decreased in CD4+ T cells from peripheral blood mononuclear cells of RRMS patients [50]. miR-124, miR-486a, and miR-532 were significantly decreased in the nucleus accumbens of chronic unpredictable mild stress-induced mice with depression-like behaviors, while miR-388 was significantly upregulated [76]. Exosomal miR-15b-5p and miR-451a were differentially expressed in 25 RRMS patients compared with 11 controls [87]. let-7b-5p is negatively associated with inflammation and disease severity in MS [95]. Upregulation of both miR-326 and miR-26a in the relapsing phase of MS patients compared with remitting phase and healthy controls was observed [41]. Let-7b, miR-20b, miR-30a, miR-125a, miR-146a, miR-221, and miR-328 were differently expressed in MS patients [24].

The miRNA profiles from active and inactive MS lesions were established by PCR in 16 active and 5 inactive white matter MS brain lesions and 9 control white matter specimens [29]. miRNAs were found at least twice more abundant or less abundant than in normal white matter in inactive lesions (see miRNAs of reference [29] in **Table 1**). Monocytes–macrophages were shown to influence the inflammatory activity and demyelination in MS. The expression of miRNAs impacting monocyte–macrophage immune function and their communication with brain cells in MS patients was investigated [21]. The levels of miR-146a, miR-223, miR-125a, and miR-30c were increased in both RRMS and PPMS patients compared with controls, and the level of miR-155 was decreased in both PPMS and RRMS patients compared with controls. In addition, reduced levels of miR-124 were observed in PPMS patients compared with controls and RRMS patients.

Blood samples from 40 RRMS patients and 20 healthy volunteers were investigated [34]. The expression levels of miR-34a, miR-199a, miR-30c, and miR-19a, and the percentage of Th17 and Treg cells were measured. An increased expression of miR-34a, miR-30c, and miR-19a in the relapsing phase and a decreased expression of miR-199a in the remitting phase were observed. A correlation was shown between the four miRNAs, miR-34a, miR-199a, miR-30c, and miR-19a, with different phases of MS, and these miRNAs were involved in differentiation pathways of Th17 cells. The association between the miRNA expression level in CSF and gadolinium-enhancing (Gd+) lesions was investigated to identify the miRNA biomarkers of MS [86]. A total of 28 miRNA candidates in CSF collected from 46 patients with MS (26 Gd+ and 20 Gd− patients) were performed by TaqMan assays and PCR. Increasing levels of miR-21 and miR-146a/b were observed in Gd+ MS patients. miRNAs related to treated MS patients were studied [43]. Eleven RRMS patients were classified into two groups: four untreated patients who had received no treatment with any disease-modifying therapy, and seven treated patients with the immunomodulatory drug IFN-β with at least a 2-year follow-up. PCR analysis showed that 16 miRNAs were differentially expressed in the two groups (see miRNAs of reference [43] in **Table 1**).

Lithium (Li) is commonly used in the treatment of bipolar disorder known as manic depression. miR-34a, miR-152, miR-155, and miR-221 were consistently upregulated in 20 lymphoblastoid cell lines with Li treatment at treatment time points day 4 and day 16 [37]. The glutamate receptor, metabotropic 4 (GRM4), that can regulate MD was an attractive target for drug discovery [31]. To investigate GRM4 regulation, an analysis showed that miR-650 and miR-328 were downregulated and upregulated in the blood samples of 18 MD patients compared with healthy controls, respectively [31]. miR-21 was reduced in the white matter of mice with MD [47]. miRNA-15a was increased in the amygdala–Ago2 complex in the mice exposing to chronic stress [53]. β-catenin has been implicated in MD. miR-214-3p was significantly upregulated in the medial prefrontal cortex of chronic social defeat stress mice by targeting β-catenin transcripts [57]. Brain-enriched miRNA-

184 is downregulated in older patients with MD [59]. MD patients had significantly increased exosomal miR-139-5p levels when compared with controls [62]. Serum expression levels of miR-23b-3p and miR-142-3p significantly increased in 102 bipolar II disorder patients compared with 118 controls [45].

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