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Review Article

An introduction to microRNAs and their dysregulation in psychiatric disorders

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ABSTRACT

MicroRNAs (miRNAs), prominent types of small noncoding RNA, have been revealed as key regulators of gene expression at the post-transcriptional level. Major advances in the understanding of miRNA biology in the past decades include biogenesis pathways, principles of target gene regulation and identification of target transcripts. Of note, miRNAs can act as a switch or a fine-tuner to control the level and function of target genes, which reciprocally regulate miRNAs via miRNA response elements at 3′ untranslated regions. In addition to current knowledge about miRNA biogenesis and function, this review looks at mounting evidence that aberrant expression of miRNAs in both the cerebral cortex and peripheral blood mononuclear cells may underlie many of the molecular changes observed in psychiatric disorders.

1. Introduction

Since the last few decades of the 20th century, the central dogma of molecular biology has been that the purpose of transcribed RNA is to direct the assembly of proteins from amino acids. Only a few exceptions to this paradigm are known. Examples include ribosomal RNA and transfer RNA, both of which are functional RNA macromolecules that do not code for protein, and viral genomes that exist as or pass through an RNA phase as part of total genome replication. However, more recent studies have uncovered thousands of RNA species transcribed in the genome that serve as regulatory elements for individual genes as well as gene networks. These RNAs are collectively known as noncoding RNAs (ncRNAs), which can interact with DNA, RNA, and protein molecules and engage in diverse structure and functional activities. They also have roles in nuclear organization, and transcriptional, post-transcriptional, and epigenetic processes. Among them, one class of small ncRNAs—the microRNAs (miRNAs)—has been found to be quite phylogenetically extensive and conservative in eukaryotic cells.

The miRNAs were first recognized as “small temporal” antisense RNAs controlling the timing of larval development in the nematode *Caenorhabditis elegans* by Lee et al in 1993 [1]. Since then, more novel genes coding for these small expressed RNAs have been identified, and the term “microRNAs” was given to them in 2001 [2–4]. Averaging 22 nucleotides (nt) in length (19–25 nt for mature miRNAs), these single-stranded RNAs, canonically derived from longer primary transcripts (pri-miRNAs), bind to sequences called microRNA response elements (MREs) with partial complementarity on target mRNA, usually resulting in the repression of target gene expression. Today, 1600 precursory genes and 2042 mature sequences of miRNAs have been identified in humans according to the latest information from a microRNA database (miRBase 19, released in August 2012). It is estimated that about two-thirds of human protein-coding genes are under selective pressure to maintain pairing to miRNAs, and are thus potential targets for miRNAs [5].

The central nervous system is characterized by extraordinary degrees of functional network connectivity and responsiveness to interoceptive and environmental stimuli. It is now clear that these features are mediated not only by the expression profiles, localization, and translation of protein-coding genes, but also by miRNAs that have a diverse range of regulatory and functional roles in

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transcriptional, post-transcriptional, epigenetic, and nuclear processes. An adequate spatiotemporal coordination of gene-regulatory networks in response to internal or external signals is crucial to the normal development and function of the brain, and inclusion of miRNAs in such regulatory mechanisms appears to increase the precision of biological functionalities of the genes [6,7]. Moreover, many novel brain-specific miRNA families have increasing diversity in nonhuman primates and humans, suggesting that miRNA evolution is an ongoing process linked to greater brain complexity [8]. In recent years, roles for specific miRNAs in neuronal development, function, and dysfunction have been demonstrated [9].

In this brief review, we summarize our current knowledge about the principles of biogenesis and biological functions of miRNAs in mammals, and then focus on evidence demonstrating the role of miRNAs in psychiatric disorders.

2. The biogenesis and turnover of miRNA

Initially, the pri-miRNA sequence is transcribed in a RNA polymerase II-dependent manner into a double-stranded RNA with a stem-loop structure. The precursor genes coding for miRNAs are frequently located in introns or intergenic regions of protein-coding genes. Other miRNAs are transcribed as part of long ncRNAs and are often arranged as clusters in the genome, which leads to one pri-miRNA being subsequently processed into several functional miRNAs. Following transcription, the RNase III endonuclease Drosha, in conjunction with Di George syndrome critical region gene 8 (DGCR8), excises the pri-miRNA stem-loop, resulting in a hairpin-shaped RNA molecule of 70–100 base pairs called an miRNA precursor or pre-miRNA [10–12]. The pre-miRNAs are specifically recognized by the nuclear export receptor Exportin 5 and exported in a Ran-GTP dependent manner [13,14].

In the cytoplasm, the pre-miRNAs are further cleaved by the double-stranded RNA binding protein transactivation-responsive RNA-binding protein and the RNase III enzyme Dicer. The result of Dicer cleavage is an miRNA/miRNA* duplex of ~22 nt in length. One strand of this duplex, the mature miRNA, is then transferred and incorporated into the miRNA-induced silencing complex (miRISC), while the other strand, the miRNA star strand (miRNA*), is released and degraded. Generally, the strand with less stable base pairing at the 5′ end is retained in the miRNA/miRNA* duplex. The miRNA* strands are not always by-products or passengers of miRNA biogenesis and can also be loaded into miRISC to function as mature miRNAs [15,16]. In mammals, the strand selection and miRISC assembly is accomplished by a complex that contains Dicer, transactivation-responsive RNA-binding protein, and argonaute (AGO) proteins [17,18].

There are a number of cofactors or accessory proteins that act as activators or repressors in the maturation of miRNAs. For example, the two DEAD-box RNA helicases DDX5 and DDX17 (also known as p68 and p72), identified as integral parts of the Drosha microprocessor complex, are thought to stimulate processing of a subset of pri-miRNAs by themselves [19] or by interacting with other proteins such as SMADs and p53 [20,21]. The presence of LIN-28, the best-studied negative regulator of miRNA biogenesis, can act at both the Drosha and Dicer levels to block the expression of mature “let-7” family miRNAs in embryonic stem cells and other progenitor cells [22]. An overview of miRNA biogenesis is shown in Fig. 1.

In contrast to miRNA biogenesis, regulation of the turnover and decay of miRNAs is still largely unknown. It is generally thought that miRNAs represent highly stable molecules, and long half-lives of certain miRNAs in cells lines or organs have been found [23]. However, such slow turnover is unlikely to be a universal feature of miRNAs as they often play a role in developmental transitions, or act as on/off switches of gene expression, conditions that require

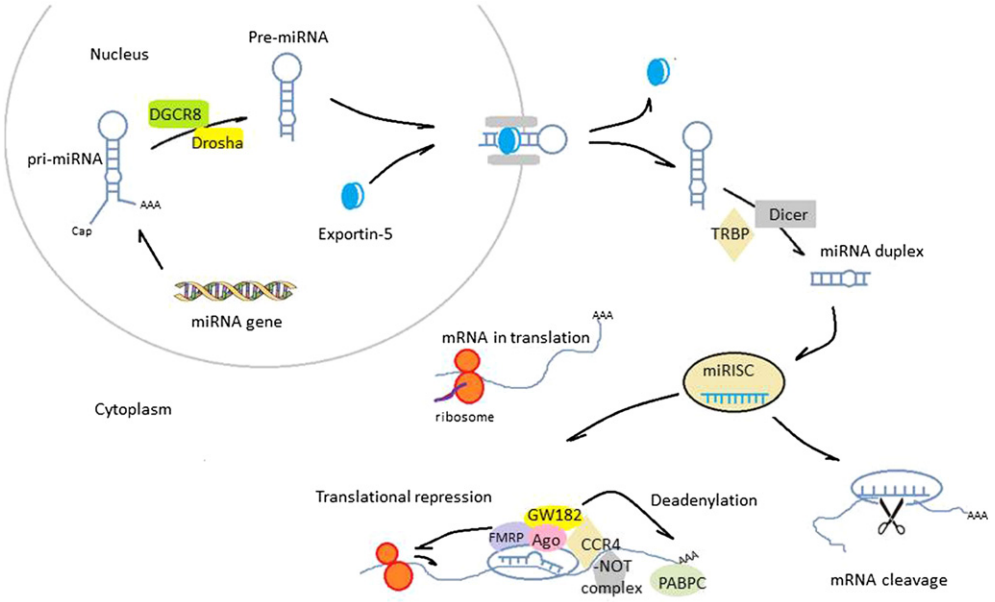

Fig. 1. Biogenesis of miRNAs. After transcription by RNA polymerase II, pri-miRNA is generated and subsequently cleaved in the nucleus by the Drosha/DGCR8 microprocessor complex. The cleavage product is a pre-miRNA hairpin, which is then exported to the cytoplasm by an Exportin 5/Ran-GTP dependent pathway. The pre-miRNA hairpin is further processed by Dicer and accessory proteins such as TRBP to a short-lived miRNA duplex intermediate. One strand is selected and becomes the mature miRNA, whereas the other is usually degraded. The mature miRNA is loaded into a multi-protein complex to generate the miRISC. With the guide of mature miRNA, the miRISC binds to specific “seed” sequences located predominantly within the 3′-UTR region of mRNAs and can interfere with translation of the mRNA and reduce mRNA levels. AGO = argonaute; DGCR8 = Di George syndrome critical region gene 8; FMRP = fragile X mental retardation protein; GW182 = glycine-tryptophan protein of 182 kDa; miRNAs = microRNAs; miRISC = miRNA-induced silencing complex; PABPC = cytoplasmic poly-A binding protein; pre-miRNA = precursor microRNA; pri-miRNA = primary microRNA; TRBP = transactivation-responsive RNA-binding protein; UTR = untranslated region.

more active metabolism. Indeed, rapid turnover and degradation of some miRNAs has been reported in mouse retinal neurons and primary dissociated neurons [24]. Notably, many, if not all miRNA turnover in neurons seems to be activity dependent, suggesting that active miRNA metabolism may be important for neuronal function [25].

3. The mechanisms of action of miRNAs

The mechanisms used by miRNAs to regulate target gene expression has been a controversial subject, as there is evidence for target messenger RNA (mRNA) destabilization and translational repression, and even activation of gene expression [26]. Regulation of target gene expression by miRNAs is subjected to various levels of control, and recent developments have added a level of complexity; targets can reciprocally control the function, stability, and expression of miRNAs. In this section, the conventional logic of target regulation by miRNAs will be discussed first, followed by an introduction to the intertwined relationship between miRNAs and the "competing endogenous" RNAs (ceRNAs).

3.1. Target regulation by miRNA

In principle, the sequence of the miRNA specifies the target mRNA sequence via perfect Watson–Crick base-pairing between nucleotides 2–8 (the seed region) of the miRNA and a complementary site in the 3′ untranslated region (UTR) of the target mRNA. The degree of complementarity between miRNA and mRNA dictates the method of gene inhibition; perfect complementarity results in AGO-mediated cleavage of the target mRNA, while mismatches result in translational repression, a reversible process that may allow cells to store mRNAs in preparation for rapid translation [27]. miRISC is the functional unit that induces miRNA-guided translational repression or deadenylation and degradation in the target mRNAs. AGO proteins, which directly interact with miRNAs, and glycine-tryptophan protein of 182 kDa (GW182), the downstream effector in translational repression and/or deadenylation, are key factors in the function of miRISC. Perfect pairing of an miRNA and its target site supports endonucleolytic cleavage of mRNA by AGO, leading to rapid degradation of the mRNA, which is a common mechanism in plants but is much rarer in animals. GW182 proteins can recruit the CCR4-NOT protein complex, which removes the poly-A tail and dissociates the cytoplasmic poly-A binding protein to make the mRNA susceptible to exonucleolytic degradation when partial pairing occurs between the miRISC and 3′-UTR sequence of the target mRNA [28]. There are also cases in which miRNAs cause reduced protein but not mRNA levels, suggesting that translation repression can be directed by miRISC. The actual mechanism that blocks protein production is not clear. Ribosome profiling, a recently developed technology to detect mRNA fragments associated with ribosomes, can provide some evidence for the inhibition of translational initiation or elongation by miRISC, as well as for directed proteolysis of the peptide being synthesized from the miRNA-targeted mRNA [29]. Recent work has shown that the CCR4-NOT complex that is recruited by GW182 to deadenylate target mRNAs also acts to repress the initiation of translation [30–32].

Stimulated translation of targets by miRNAs has been reported under certain circumstances [33,34]. For example, in conjunction with the proteins AGO and FMRP (fragile X mental retardation syndrome-related protein), miR-16 targets *myt1* kinase mRNA and activates its expression in *Xenopus laevis* oocytes [35]. A recent study showed that miR-328 directly interacts with hnRNP E2, a regulatory RNA binding protein, preventing it from blocking translation of C/EBPα mRNA [36]. In this case, rather than serving as the guiding part of miRISC that decays its target, miR-328 acts as a decoy to suppress the translational inhibitor hnRNP E2 and restore translation of the hnRNP E2-targeted mRNAs. Overall, miRNAs typically repress gene expression; whether positive regulation of targets extends beyond the limited cases uncovered so far remains to be seen.

In view of the regulatory mechanisms mentioned above, it seems that miRNAs behave as a switch in target gene expression. In fact, the typical magnitude of observed gene repression by miRNAs is relatively small [37,38]. Mukherji et al performed single-cell measurements and found that miRNAs can generate thresholds in target gene expression [39]. When the relative expression of the target gene is below the threshold, its protein production is highly repressed. Near this threshold, the protein expression responds sensitively to target mRNA input, which fits a molecular titration model. Therefore, miRNAs can behave both as a switch in the target expression regime below the threshold, and as a fine-tuner in the sensitive transition between the threshold and the minimal repression regime at relatively high mRNA levels.

3.2. Regulation of miRNAs by target interactions

Regulation in the miRNA pathway is a two-way street—not only can base pairing between an miRNA and its target result in repressed target expression, but these interactions can also have an impact on the levels of the miRNA. For example, artificial "miRNA sponges" using multiple copies of a single MRE in tandem effectively knock down the miRNA family sharing the same seed region and derepress miRNA targets [40]. There are also "endogenous" or "natural" sponges in cells from transcribed RNAs that contain MREs. Actually, all miRNA targets, including coding and noncoding transcriptomes, can be endogenous sponges of miRNAs.

Besides regulating the stability of miRNAs via direct base-pairing interactions, these sponges can influence one another's level by competing for a limited pool of miRNAs. Salmena et al proposed a hypothesis of ceRNA to describe how mRNAs, transcribed pseudogenes and ncRNAs "talk" to each other using MREs as letters of a new language [41]. By presenting target sites for the same miRNAs, ceRNAs mutually regulate each other's expression and form a large-scale regulatory network across the transcriptome. Experimental evidence supporting the ceRNA hypothesis includes the observation that overexpression of the 3′-UTR of PTENP1, the pseudogene of phosphatase and tensin homolog (PTEN) tumor suppressor gene, increases levels of PTEN and growth inhibition in a DICER-dependent manner [42]. That is, PTENP1 is biologically active as it can regulate cellular levels of PTEN and exert a growth-suppressive role by acting as a decoy for PTEN-targeting miRNAs. Another example in *Arabidopsis thaliana* demonstrated that the ncRNA phosphate starvation 1 sequesters miR-399 and results in attenuation of miR-399-mediated protein-coding gene degradation by mimicking its target site, a phenomenon called "target mimicry" [43]. Large-scale analysis of gene expression and matched miRNA profiles in human gliomas also lend support to the idea that thousands of transcripts may be acting as miRNA target decoys [44]. Notably, the ceRNA hypothesis may help explain the recently identified expression of distinct RNAs from 3′-UTRs [45]. Instead of acting as *cis*-regulatory elements that alter the stability of their own transcripts, 3′-UTRs may act in *trans* to modulate gene expression through miRNA binding. As proposed by the ceRNA hypothesis, events that can alter the abundance or sequence of a particular transcript are possible to induce "coding-independent" effects via interactions with miRNAs and contribute to the pathological process of diseases (Fig. 2).

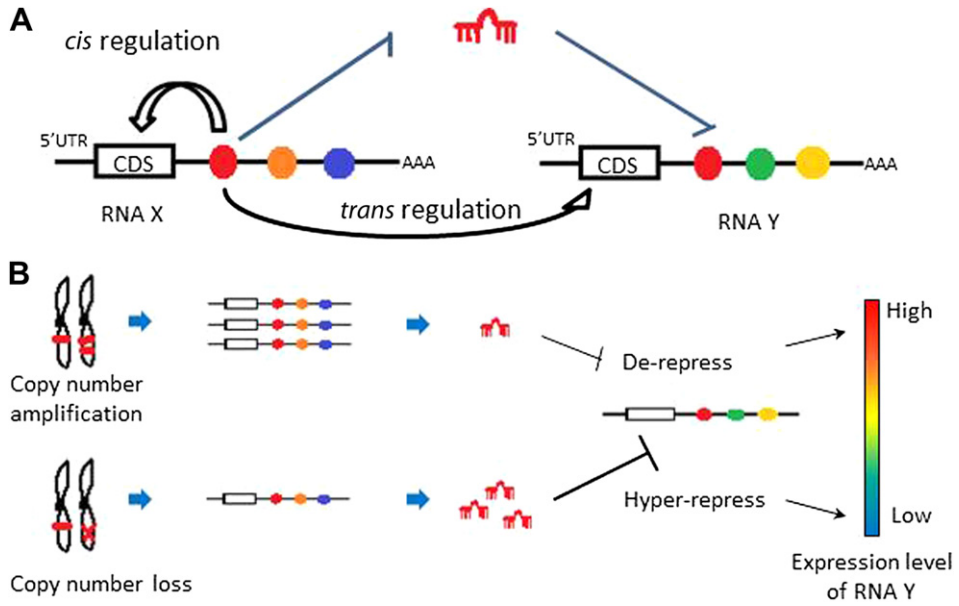

Fig. 2. ceRNA logic and coding-independent regulation. (A) RNA molecules can communicate with each other through miRNA and MREs at 3′-UTRs. For example, one of the MREs (red circle) at the 3′-UTR of RNA X can not only function in *cis* to regulate RNA X itself but also in *trans* to regulate RNA Y that shares similar MREs by the same acting miRNA. RNA X and Y are acting as ceRNA mutually. (B) Genomic alterations such as copy number variations can alter the abundance of a particular transcript, and these events are possible to induce "coding-independent" effects (e.g., up- or downregulation of other transcripts) by altering the levels of shared miRNAs. ceRNA = competing endogenous RNA; miRNAs = microRNAs; MREs = miRNA response sequences; UTRs = untranslated regions.

4. miRNA dysregulation in psychiatric disorders

Psychiatric disorders, including schizophrenia, autistic disorders, mood disorders (e.g., bipolar and depressive disorders), and anxiety disorders (e.g., panic, phobic, and post-traumatic stress disorders), are a major burden on both patients and society. The ability of miRNAs to have a broad effect on gene regulation and functional pathways has important implications for psychiatric disorders, which have been characterized by complex genetics and multi-pathway dysregulation. Recent studies on miRNA expression profiling of brain tissue and peripheral blood from patients with schizophrenia and bipolar disorder, as well as studies using animal behavioral models to explore the molecular mechanisms of some candidate miRNAs in psychosis, have indicated that miRNAs may serve as disease biomarkers and represent new therapeutic targets in psychiatry (Table 1).

4.1. miRNA dysregulation in schizophrenia

Several studies have examined the expression profiles of miRNAs in *postmortem* gray matter of individuals with schizophrenia utilizing a case–control approach [46–52]. Collectively, these studies have identified many dysregulated miRNAs associated with schizophrenia. However, while some have displayed consistent changes across independent studies, many others have not. A total of 16 miRNAs have been associated with consistently increased expression (miR-105, miR-128a, miR-15a/b, miR-16, miR-17, miR-199a*, miR-20a, miR-222, miR-34a, miR-452*, miR-486, miR-487a, miR-502, miR-652, miR-7) and 11 miRNAs with consistently decreased expression (miR-106b, miR-151, miR-20b, miR-224, miR-30a/b/d/e, miR-383, miR-432, miR-505) in multiple studies using human postmortem brains. Some miRNAs, such as miR-212, and miR-26b, are consistently reported to display significantly altered expression, except in opposing directions [53]. The discrepancies in the results can be attributed to technical variations such as tissue preparation, sampling region differences, RNA isolation methods, amplification, array platform, chemistry, and normalization methods. In addition, the type and duration of antipsychotic medication, genetic heterogeneity and diagnostic instability are factors that certainly could account for the bias among different studies.

Investigation of miRNAs from peripheral blood mononuclear cells (PBMCs) is a potential clinical application in schizophrenia. First, PBMCs are more homogenous than brain tissue and can be collected in large numbers from living patients. Second, although the major disordered organ in schizophrenia is the brain, it is plausible that the miRNA expression signature in PBMCs may reflect not only disease-associated systemic changes but also immunological risk factors relevant to the underlying biological mechanism of schizophrenia. Using the expression profiles of PBMCs, a research group from Taiwan identified peripheral patterns of miRNAs that could have utility as biomarkers for schizophrenia and associated endophenotypes [54]. Last but not least, PBMCs are a common source for DNA isolation and subsequent gene sequence and genome structure studies. Thus, experiments in genetic linkage, genome-wide association studies (GWAS) and copy number variations can be carried out with the same samples from miRNAs expression studies. Gardiner et al applied this method and revealed that a subgroup of dysregulated miRNAs were transcribed from a single imprinted locus at the maternally expressed DLK1-DIO3 region on chromosome 14q32 [55].

Individuals with 22q11.2 microdeletions are at high risk of developing schizophrenia. With a cognitive deficit mouse model, Stark et al showed that abnormal miRNA biogenesis due to DGCR8 gene haploinsufficiency played a key role in a 22q11-deletion [56]. A number of studies have tested the association of miRNA polymorphisms or tag single nucleotide polymorphisms (SNPs) and schizophrenia [57–59], and perhaps the most exciting miRNA gene to show genetic association in a recent "mega-analysis" of GWAS was miR-137 [60]. The functional significance of miR-137 susceptible variants in schizophrenia and other mental illnesses have also been surveyed with consistent impacts on neural abnormalities and cognitive deficits [61–64]. In miR-137 studies for example,

integrated analysis of the results from GWAS, functional brain images, and *in vitro* and *in vivo* disease model studies could shed some light on the roles and mechanisms of miRNA dysregulation in schizophrenia.

4.2. miRNA dysregulation in autism and mood and anxiety disorders

Similar to schizophrenia, dysregulation of miRNAs has been investigated in other major psychiatric disorders such as autism, bipolar and unipolar depression, and anxiety but there are fewer reported studies (Table 1). To identify a set of differentially expressed miRNAs in autistic patients, Abu-Elneel et al used *postmortem* cerebellar cortex tissue [65], while Talebizadeh et al and Sarachana et al used lymphoblastoid cell lines (LCLs) derived from independent case–control cohorts [66,67]. The upregulation of miR-23a was the only finding in common in these three studies. Moreau et al revealed more pronounced underexpression of 24 miRNAs in the prefrontal cortex of patients with bipolar disorder than in schizophrenic and healthy control groups [51]. Similarly, Smalheiser et al reported that 21 miRNAs were significantly downregulated in the prefrontal cortex of depressed suicide subjects [68]. Using SNPs tagging human miRNA regions, Muiños-Gimeno et al reported the first study that showed miR-22, miR-138-2, miR-148a, and miR-488 were associated with panic disorder, one of the anxiety disorders, in Spanish and Finnish patients [69].

In addition to traits or states of diseases, the therapeutic effects of psychotropic medications may also be mediated by miRNAs. Zhou et al found that *in vitro* lithium and valproic acid treatment differentially regulated 37 and 31 miRNAs, respectively, with eight

Table 1
MicroRNAs associated with psychiatric disease.

Disease	Study material/methods	Species	Disease-associated miRNA (miR-)	Reference
Schizophrenia	Postmortem brain (DLPFC,BA9)/microarray	Human	Up-regulated: 106b Down-regulated: 7, 20b, 24, 26b, 29a, 29b, 29c, 30a, 30b, 30d, 30e, 92, 195, 212, 9*	[46]
	Postmortem brain (STG,BA22)/microarray	Human	Up-regulated: 181b	[47]
	PFC and HPC of 22q11.2 hemizygous deletion/microarray	Mouse	Down-regulated: 185, 134, 674, 540, 106b, 140*, 194, 325, 494, 362, 409, 323, 669a, 151, 18, 532, 673, 674*, 224, 491, 93, 383, 212, 422b, 708	[56]
	Postmortem brain (STG,BA22)/microarray	Human	Up-regulated: let-7e, 107, 125b, 128a, 128b, 129, 130a, 133b, 138, 146b, 148a, 150, 152, 155, 15a, 15b, 16, 17-3p, 17-5p, 181b, 195, 197, 199a*, 19a, 20a, 222, 23a, 24, 26b, 27b, 28, 296, 328, 330, 335, 338, 339, 340, 373*, 381, 409-5p, 432*, 452*, 455, 484, 485-5p, 486, 487a, 489, 494, 499, 502, 517a, 517c, 518b, 519d, 520a*, 520g, 9*, 99a	[49]
	Postmortem brain (DLPFC,BA9)/microarray	Human	Up-regulated: let-7d, 101, 105, 107, 126*, 128a, 153, 15a, 15b, 16, 181a, 181b, 181d, 184, 195, 199a, 20a, 219, 223, 26b, 27a, 29c, 302a*, 302b*, 31, 33, 338, 409-3p, 512-3p, 519b, 7	[49]
	Blood (59 X-linked miRNA genes)/resequencing	Human	X-linked private mutations in schizophrenia: 7f-2, 188-3p, 325-3p, 509-3p, 660	[57]
	Postmortem brain (PFC,BA10)/microarray	Human	Down-regulated: 30e, 195	[48]
	Postmortem brain (DLPFC,BA46)/Tagman low density array	Human	Up-regulated: 132, 132*, 154*, 212, 34a, 544, 7	[50]
	PBMCs/microarray	Human	Up-regulated: 34a, 449a, 548d, 564, 572, 652 Down-regulated: 432	[54]
	PBMCs/microarray	Human	Down-regulated: 107, 134, 31, 431, 433, 487b, 99b	[55]
	Postmortem brain (DLPFC,BA9)/realtime qPCR (Taqman assay)	Human	Up-regulated: 193b, 545, 639 Down-regulated: 33, 106b, 138, 151, 210, 22, 324-3p, 338, 339, 425	[51]
	Postmortem brain (DLPFC,BA46)/microarray	Human	Up-regulated: 328, 17-5p, 134, 652, 382, 107	[52]
	NA./mega-analysis of GWAS	Human	Risk loci: 137	[60]
Bipolar disorder	Postmortem brain (DLPFC,BA46)/Tagman low density array	Human	Up-regulated: 133b, 145, 145*, 154, 22*, 504, 889 Down-regulated: 32, 140-3p, 29a, 874, 454*, 520c-3p, 573, 767-5p	[50]
	Postmortem brain (DLPFC,BA9)/realtime qPCR (Taqman assay)	Human	Down-regulated: 33, 330, 192, 193a, 193b, 545, 138, 151, 210, 324-3p, 22, 425, 181a, 106b, 301, 27b, 148b, 338, 639, 15a, 186, 99a, 190, 339	[51]
	HPC, after long-term lithium and valproate administration/microarray	Rat	Up-regulated: 144 Down-regulated: 34a, let-7b, let-7c, 30c, 128a, 221, 24a	[70]
	LCLs from bipolar patients, after 4-day lithium tx/realtime qPCR (Taqman assay)	Human	Up-regulated: 15a, 152, 221 Down-regulated: 494	[71]
Autism	LCLs from autistic subjects/microarray	Human	Up-regulated: 23a, 23b, 132, 146a, 146b, 663 Down-regulated: 92, 320, 363	[66]
	LCLs from autistic subjects/microarray	Human	Up-regulated: 185, 103, 107, 29b, 194, 524, 191, 376a, 451, 23b, 195, 342, 23a, 186, 25, 519c, 346, 205, 30c, 93, 106b Down-regulated: 182, 136, 518a, 153, 520b, 455, 326, 199b, 211b, 132, 495, 16, 190, 219, 148b, 189, 133b, 100b, 367, 139	[67]
Panic disorder	NA (case-control from Spanish, Finnish & Estonian)/miR-SNP	Human	Risk loci: 22, 339, 138-2, 148a, 488	[69]

BA = Brodmann's area; DLPFC = dorsolateral prefrontal cortex; GWAS = genome-wide association study; HPC = hippocampus; LCLs = lymphoblastoid cell lines; miR-SNP = single nucleotide polymorphisms tagging microRNA; PBMCs = peripheral blood mononuclear cells; PFC = prefrontal cortex; STG = superior temporal gyrus.

miRNAs in common [70]. Chen et al examined miRNA expression in LCLs derived from bipolar patients and unaffected siblings, and identified alterations in the expression of several miRNAs following lithium treatment [71]. Fluoxetine (Prozac), a well-known selective serotonin reuptake inhibitor antidepressant was recently shown to increase miR-16 levels in serotonergic raphe nuclei, which targets the serotonin transporter and promotes hippocampal neurogenesis [72,73]. Taken together, investigations of dynamic changes of miRNA expression during disease progression and recovery may provide more insight into the underlying pathophysiology of psychiatric disorders, and new therapeutic targets as well [74].

5. Summary and future directions

The ability of miRNAs to fine-tune and switch the activity of entire biological pathways makes them key regulators in a range of biological processes, including cell fate determination, tissue differentiation and organismal development. It is noteworthy that the biological influences of miRNAs are not restricted to processes within cells: they can act inside a cell between cellular organelles and compartments, or outside cells between different tissues and systems, and even outside living organisms between different kingdoms. For example, nuclear miR-181c can translocate into the mitochondria and regulate mitochondrial genome expression in cardiac myocytes [75], while exogenous plant miRNAs in food (e.g., miR-168a from rice) can regulate the expression of target genes in mammals [76]. The full scope and power of the biological influences of miRNAs and other ncRNAs remain to be seen.

The diagnosis of psychiatric disorders is currently based exclusively on behavioral signs and symptoms assessed by qualified psychiatrists. Using a molecular signature could not only refine a diagnosis but also facilitate earlier intervention. Peripheral miRNA-based biomarkers have already been shown useful in the clinical stratification of cancer and have even greater prognostic significance than mRNAs [77]. Moreover, a recent study showed that miRNAs could induce conversion of human fibroblasts to neurons [78], which would be a promising way to obtain neuronal tissues from patients with neuropsychiatric disorders to help development of novel drugs. Studies on miRNA dysregulation are increasing rapidly, and this emerging field is anticipated to affect clinical research, diagnosis, and therapy in psychiatry profoundly. Future work will be necessary to unravel a more complete picture of dysregulated miRNAs and test their potential for clinical applications in psychiatric disorders.

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