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Current Update on Synopsis of miRNA Dysregulation in Neurological Disorders

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Abstract

Aberrant expression of microRNAs (miRNAs) has been implicated in various neurological disorders (NDs) of the central nervous system such as Alzheimer disease, Parkinson's disease, Huntington disease, amyotrophic lateral sclerosis, schizophrenia and autism. If dysregulated miRNAs are identified in patients suffering from NDs, this may serve as a biomarker for the earlier diagnosis and monitoring of disease progression. Identifying the role of miRNAs in normal cellular processes and understanding how dysregulated miRNA expression is responsible for their neurological effects is also critical in the development of new therapeutic strategies for NDs. miRNAs hold great promise from a therapeutic point of view especially if it can be proved that a single miRNA has the ability to influence several target genes, making it possible for the researchers to potentially modify a whole disease phenotype by modulating a single miRNA molecule. Hence, better understanding of the mechanisms by which miRNA play a role in the pathogenesis of NDs may provide novel targets to scientists and researchers for innovative therapies.

Keywords

Alzheimer disease; amyotrophic lateral sclerosis; autism; Huntington disease; microRNA; neurodegeneration; Parkinson's disease; postmortem brain tissue; schizophrenia

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

BACKGROUND

Neurological disorders (NDs) of the central nervous system collectively refer to a group of diseases characterized by psychiatric features associated with brain malfunction or, in many cases, neurobehavioral symptoms characterized by the progressive loss of neuronal function and structure, ending in death of neurons. Depending on the brain region and type of neurons affected, NDs include Alzheimer disease (AD), Parkinson's disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), schizophrenia and autism. With advancement in research and knowledge, there has been increasing evidence showing that NDs appear to share common biological mechanisms at the sub-cellular level. Discovering shared mechanisms in NDs offers hope to find therapeutic solutions that may treat many of those disorders at the same time. One such common mechanism is dysregulation of microRNAs (miRNAs) which contributes to neurodegeneration by influencing potential responsible for causing NDs. Thus, neurological disorders can be regarded as a type of "RNA disorder" in which miRNAs play a pivotal role [1].

miRNA refers to a small non-coding, single stranded RNA molecule comprising of around 22 nucleotides. By base pairing to messenger RNA (mRNA) and triggering translation repression, the miRNAs control gene expression [2]. miRNAs were first characterized in the early 1990s [3]. However, their role as a specific category of biological regulators with conserved functions was not fully realized until a decade later. Current miRNA research has revealed that miRNAs are possibly involved in almost all biological processes by modifying and modulating the expression of thousands of genes, hence affect the gene regulation [4–7]. The human genome consists of more than 1000 miRNAs. Interestingly, miRNA dysregulation has been implicated in various NDs. Consequently, cell culture assays and knockout models have been generated to get a better understanding of the pathways regulated by specific miRNAs in the body. Autopsy brain findings and animal studies have shown that close to 70% of the identified miRNAs are expressed in the central nervous system with a distinct localization [8]. With better understanding of the role of miRNAs in neurodegenerative diseases, scientists and researchers may create effective new drugs to treat these devastating human illnesses [9]. The goal of this paper is to provide a brief synopsis of dysregulation of miRNAs in NDs such as AD, PD, HD, ALS, schizophrenia and autism.

OXIDATIVE STRESS AND DYSREGULATION OF miRNA IN NEUROLOGICAL DISORDERS

Increasing evidence suggests that oxidative stress significantly contributes towards deregulated miRNA pathways during the development of the NDs. Oxidative stress has been shown to be not just a byproduct of neuronal deterioration but also an instigating factor in causing neurodegeneration [10–13]. RNAs are among the nucleic acids that have been shown to be damaged by reactive oxygen species. Changes in RNA as a result of oxidative stress have been associated with selective neuronal degeneration in mammalian brains [14]. Compared to normal aging brains, significant neuronal RNA oxidation has been associated with NDs such as AD, PD, dementia with Lewy bodies and AML [15]. In neurological disorders such as AD, abnormally increased nucleic acid oxidation has been observed,

implicating the potential role of oxidative stress in deregulation of miRNA pathways [16]. It has also been shown that ribosomal RNA in AD is oxidized by the bound redox- active iron, indicating neurodegeneration [17]. Likewise, miRNAs expression profile is affected by oxidative stress. For instance, when the effect of oxidative stress induced by tertiary-butyl hydroperoxide on mouse testis miRNA expression was explored, it was found that three out of five selected miRNAs, specifically, miR-122a, miR-181b and miR-34a, underwent changes. In addition to their role in spermatogenesis arrest, miR-122a, miR-181b and miR-34a also play a pivotal role in antioxidant responses and inflammation pathways [18].

More importantly, the effects of oxidative stress on miRNA expression have been studied in primary hippocampal neurons. In one study, microarray analysis of hydrogen peroxide-challenged hippocampal neurons and different strains of aging accelerated mice showed upregulation of miRNAs, specifically, miR-20a, miR-130b, miR-193b, miR-296 and miR-329 [19]. Analysis of these co-regulated miRNAs in the Kyoto Encyclopedia of Genes and Genomes Pathway revealed that the 83 target genes of miR-20a, miR-130b, miR-193b, miR-296 and miR-329 were involved in regulation of cell growth, neuron signal transmission and apoptosis, suggesting the role of deregulated miRNAs in neurodegeneration [19]. In another study, oxidative-stress challenge of mouse primary hippocampal neurons caused deregulation of several miRNAs. Among those deregulated miRNAs, two significantly up-regulated miRNAs were miR-708 and miR-135b which were found to play a crucial role in protein ubiquitination, DNA recombination, protein auto-phosphorylation and neuronal development, strongly implicating the role of deregulated miRNAs in neurodegenerative disorders such as AD [20]. All these results suggest that oxidative stress has the potential to change the expression profile of miRNAs and the resulting deregulation of miRNAs may contribute to the pathogenesis of neurological disorders, although there is still a need to further investigate the underlying mechanisms of deregulation of miRNA due to oxidative stress (Table 1).

DYSREGULATION OF miRNA IN ALZHEIMER DISEASE (AD)

Alzheimer disease (AD) is the most prevalent memory disorder among the neurodegenerative diseases, and one of the major diseases afflicting the aging population. Patients suffering from AD ultimately become totally disabled and die earlier than normal. There are close to 30 million people worldwide who suffer from AD and the number is expected to be increasing in the coming years [21]. It has been projected that the prevalence rates of AD are expected to double every 20 years in the future [22]. AD is characterized by progressive loss of memory, behavior and cognitive abilities due to neuronal deterioration. Accumulated β -amyloid deposits, neurofibrillary tangles and neuronal demise in the brain are the pathological hallmarks of AD [23, 24]. Abnormal accumulation of β -amyloid peptide in the brain causes defective synaptic functions [25, 26]. β -amyloid plaque accumulation in the brain has also been shown to induce vascular endothelial damage and neurodegeneration through generation of superoxide free radicals [27, 28]. Recently, the focus of research on AD has moved from plaque formation to earlier events in AD pathogenesis such as deregulation of genes, the impact of which has yet to be determined [29]. For instance, when postmortem human brains of AD patients were profiled, significant changes in miRNA expression were observed in many brain regions [30]. Thus, changes in the expression of

miRNA in AD have been explored in different studies in order to understand the pathogenesis and progression of AD. In fact, certain miRNAs have been shown to be associated with altered regulation of certain genes known to be causative factors of AD. miRNAs that have been consistently identified to be dysregulated in AD include miR-146, miR-106, miR-9, miR-29, miR-107, miR-181 and miR-34 [31].

Amyloid precursor protein (APP) is a membrane protein found in highest concentrations in the synapses of neurons. Although APP is involved in functions such as neural plasticity and regulation of synapse formation, APP acts as the precursor molecule which, upon proteolysis, generates β -amyloid, a naturally occurring predominantly 40 amino acid long polypeptide. However, when the proportion of longer, more neurotoxic form (42 amino acids long) of β -amyloid peptide increases, it results in plaque deposition found in the brains of AD patients. APP has been reported to be a target for miRNA dysregulation in AD. Direct binding of miR106a and miR106b to APP mRNA and the subsequent downregulation of these miRNAs was seen in the anterior temporal cortex of AD subjects [32, 33]. Likewise, it has been demonstrated experimentally that addition of β -amyloid to primary neuron cultures results in a rapid decline in the levels of miR-9, suggesting that plaque formation is associated with deregulation [34].

In one small study, the abundance of miRNAs in the hippocampal region of fetal, control adult and AD patient brains were examined using fluorescent miRNA array. Enhanced levels of miR-9, miR-125b, and miR-128 were found in the hippocampus of AD patients compared to healthy controls. This data supports the hypothesis that abnormal miRNA-mediated processing of mRNA populations may play a pivotal role in the anomalous mRNA abundance and neural impairment observed in AD brain [35]. Likewise, downregulation of miR-210 and miR-9 and upregulation of miR-125b have been identified in AD patient brains suggesting that deregulated brain miRNAs can serve as biomarkers for pathways in AD pathogenesis such as neurogenesis, β -amyloid processing and insulin resistance [36]. Similarly, miRNA expression was studied in peripheral blood mononuclear cells in a study conducted on sixteen AD patients and sixteen normal elderly controls. Higher miRNA expression in peripheral blood mononuclear cells has been noted in AD patients compared to healthy controls suggesting that induction of miRNA expression in peripheral blood mononuclear cells may contribute to the abnormal systemic decline in mRNA levels in sporadic AD [37].

Since the expression of disease-coding genes may be regulated by specific miRNAs, it has been proposed that changes in miRNA expression may result in the accumulation of disease-causing proteins and subsequent neuronal degeneration in AD [38]. In one study, miRNA expression changes were measured on human brain tissues which were classed into four separate groups: elderly nondemented with insignificant AD-type pathology, mild cognitive impairment with moderate AD pathology, nondemented with early AD pathology, and individuals with AD. When mRNA expression profiling was conducted on those nondemented, mild cognitive impairment, and AD patient brains, it was found that beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1) mRNA levels were rising as miR-107 levels were decreasing with the progression of AD in the samples, indicating that miR-107 may accelerate disease progression through regulation of BACE1 [39].

Interestingly, a decline in miR-107 levels in this study was noted even in individuals with mild cognitive impairment, suggesting that reduced expression of miR-107 becomes noticeable in the earliest stages of AD. In this study by Wang *et al.*, a difference was noted in the expression of other miRNAs (e.g. miR-103) between non-demented and AD patients, but it remained constant in different clinical stages of AD.

Inflammation plays an important role in the pathogenesis of AD and other neurodegenerative diseases. There has been increasing evidence suggesting an association between inflammation and the pathogenesis of AD through processes such as microglial activation, β -amyloid accumulation, release of proinflammatory cytokines and reactive oxygen species [40, 41]. Accordingly, evidence suggests that miR-146a plays a crucial role in the development and progression of AD due to its involvement in the inflammatory signaling and progressive upregulation of inflammatory gene expression. miR-146a is upregulated specifically in those brain areas which are known to be affected in AD, including the temporal cortex and hippocampus [42, 43]. This implies that anti-miR-146a may have potential to repress the upregulation effects of miR-146a. Indeed, it has been proposed that anti-miR-146a should be used in transgenic mouse models as a first step towards anti-miR-146a clinical trials for AD due to its therapeutic potential for AD [44] as a proof of principle. It is interesting to note that miR-146a has been shown to target transmembrane spanning tetraspanin 12, which is a key regulator of ADAM10 (a disintegrin and metalloproteinase 10), a secretase enzyme that processes APP; thereby implicating the potential effect of miR-146a upon β -amyloid metabolism [45]. These findings suggest that miRNAs have impact on several mechanisms involved in the pathogenesis of AD.

DYSREGULATION OF miRNA IN PARKINSON'S DISEASE (PD)

Parkinson's disease is the second most common neurodegenerative disease and manifests as a movement disorder that affects 1% – 3% of the population above 65 years of age, with global prevalence of 4.1 to 4.6 million affected people [46, 47]. PD leads to progressive deterioration of brain functions and an early death [48]. Clinical manifestations of PD include slow movements of voluntary muscles, tremor, rigidity and ultimately postural instability [49]. The Substantia nigra is a brain structure located in the midbrain and plays an important role in body movement. PD is characterized by death and loss of dopaminergic neurons (DNs) of substantia nigra. This loss of neurons soon impacts to other brain regions, including the cingulate gyrus, amygdala as well as higher cortical regions, with symptoms manifesting in the form of psychosis and dementia. PD symptoms show high degree of variability due to significant heterogeneity of the disease itself [50]. No complete cure is presently available for PD, and the current therapies only provide symptomatic relief. Existing PD treatments include surgical therapy or medications to augment the dopaminergic system or new experimental drugs such as anti-inflammatory drugs.

miRNAs may play an important role in the treatment of PD due to the fact that quantitative recognition of certain pathogenic proteins in certain neuronal populations is pivotal for the survival of neurons involved in the pathogenesis of PD [51]. Cell culture data as well as *in vivo* experiments have demonstrated that DNs rely heavily on a functional miRNA network. In one study investigating the role of miRNAs in mammalian midbrain DNs, it was found

that miR-133b is specifically expressed in midbrain DN of healthy individuals but midbrain tissue from PD patients completely lacks this type of miRNA. It has been suggested that the maturation and functioning of midbrain DN is regulated by miR-133b through a negative-feedback circuit, which includes paired-like homeodomain transcription factor Pitx3 [52].

Alpha-synuclein (α -synuclein) is a protein found primarily at the tip of neurons in the presynaptic terminals. Parkinson's disease is characterized by abnormal accumulation of α -synuclein aggregates to form insoluble fibrils [53]. Comparative sequence analysis of α -synuclein gene has revealed that the entire 3'-untranslated region of human α -synuclein gene is highly conserved, suggesting a role of miRNA regulation [54]. So far, miR-7 and miR-153 are the only two miRNAs that have been shown to directly target α -synuclein. These two brain-enriched miRNAs bind to the 3'-untranslated region of α -synuclein and downregulate its mRNA and protein levels, with additive effects [55]. Furthermore, *in vitro* studies have revealed that miR-7 has the potential to suppress α -synuclein-induced cytotoxicity in neuronal cell models [56]. In terms of dysregulation of miRNAs, analysis of brain tissues of PD patients has revealed the presence of certain miRNAs that are significantly elevated. miR-21*, miR-26b, miR-224, miR-373*, miR-301b and miR-106b are those miRNAs in PD brain tissues that target parts of the chaperone-mediated autophagy pathway [57]. Impairment of this pathway has been proposed to disrupt α -synuclein protein degradation, hence contributing to Lewy body pathology [58].

Some studies have looked at the presence of specific miRNAs as effective biomarkers in PD patients *versus* control individuals. In one study, peripheral blood samples from eight untreated PD patients were compared with eight healthy, control subjects. Quantitative reverse transcription polymerase chain reaction analysis revealed lower expression levels of three miRNAs (miR-1, miR-22* and miR-29a) in PD patients' blood samples compared to control subjects [59]. Another study conducted similar analysis on plasma collected from 31 untreated PD patients and 25 healthy, control individuals and reported the presence of seven over-expressed miRNAs (miR-125a-3p, miR-137, miR-181c, miR-193a-3p, miR-196b, miR-331-5p, and miR-454) in PD patients, thus highlighting these miRNAs as potential PD biomarkers [60].

DYSREGULATION OF miRNA IN HUNTINGTON'S DISEASE (HD)

Huntington disease (HD) is a genetic NDD that results in degeneration of the nerve cells, resulting in debilitation, loss of muscle coordination, cognitive decline and earlier deaths [61]. As the disease progresses, uncoordinated jerky body movements become more obvious, along with cognitive deterioration, psychiatric problems and dementia. In addition, during the course of HD, there is significant deterioration of the corpus striatum and degeneration of other brain regions such as caudate nucleus, putamen and globus pallidus and even the cortex itself [62]. The cause of neuronal death in HD brains is attributed to the toxicity caused by the presence of mutant protein of the Huntington gene (Htt) and the loss of neuroprotective effects of the corresponding wild-type protein [63]. The aggregates of the mutant Htt protein, the pathological hallmark of HD, remain localized to neuronal cells, despite the fact that Htt is expressed ubiquitously in the body [64]. Currently, no cure is available for HD and existing treatments only provide symptomatic relief.

Although not much is known about the function of Htt, it has been recently reported that formation of processing bodies (P bodies) is inhibited by mutant Htt by the latter's interaction with Ago1 and Ago2, which play an important role in miRNA biogenesis [65]. This suggests the presence of miRNA deregulation in the brains of HD patients. Likewise, in another study, a cell line over-expressing mutant Htt-Exon-1 was developed and its miRNA microarray analysis was performed in HD as well as control plasma to identify miRNA biomarkers in HD. The presence of miR-34b was found to be significantly raised in response to mutant Htt-Exon-1, and this blockade changed the toxicity of mutant Htt-Exon-1 *in vitro* [66]. This study suggests that miR-34b may serve as a potential biomarker of HD prior to the onset of disease symptoms.

miRNA profiling studies undertaken on animal models, human tissues and cell-based assays have demonstrated that miRNA dysregulation in HD is extensive. For instance, an animal model study reported that the miR-200 family of miRNAs is modified in the cortex of the mutant Htt mouse model at the early stage of HD progression. Significant alteration of miR-200a and miR-200c expression in the cerebral cortex and the striatum of the mutant HD mice was noted, suggesting that modified expression of miR-200a and miR-200c may interrupt the biogenesis of proteins involved in synaptic plasticity, neurodevelopment and neuronal survival [67]. In a cell-based model of HD, the expression of miR-125b, miR-146a, and miR-150 are downregulated while miR-34b was found to be elevated in the presence of Htt protein [66]. Further studies revealed that miR-125b, miR-146a, and miR-150 targeted Htt and modulated mutant Htt aggregate formation by interacting with tata binding protein, a general transcription factor that binds specifically to DNA sequences [68]. The exact mechanism as to how this contributes to the pathogenesis of HD needs to be elucidated by further studies [69].

DYSREGULATION OF miRNA IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis (ALS), also called “Lou Gehrig’s Disease”, is a progressive and fatal NDD that affects nerve cells within the brain and spinal cord. Motor neurons extend from brain to the spinal cord and then to muscles of the whole body. Progressive degeneration of the motor neurons results in abnormal functioning of muscle tissues, causing myasthenia, dysphagia, atrophy and, eventually, loss of control of all muscles responsible for voluntary movements. About 5% of ALS patients may also develop frontotemporal dementia while the majority of ALS patients undergo subtle cognitive changes [70]. ALS eventually results in total paralysis of patients. Respiratory failure is the most common cause of death, occurring within five years of the onset of ALS symptoms. In fact, the median survival period from the onset of ALS to death is about 39 months, and only 4% of ALS patients survive more than 10 years [71]. Treatment options are few and are only symptomatic.

With the emerging role of miRNAs in NDs, several recent research efforts have explored the role of miRNAs in the pathogenesis of ALS. In order to investigate disease-specific changes in miRNAs at early stages of sporadic ALS, miRNA profiling was conducted on leukocytes obtained from blood of sporadic ALS patients [72]. In this study, blood was collected from 8

ALS patients and 12 healthy subjects, and leukocytes were isolated and screened for the expression of more than 900 human miRNAs using microarray technology. It was found that 8 miRNAs (miR-149, miR-328, miR-338-3p, miR-451, miR-583, miR-638, miR-665, and miR-1275) were found to be significantly deregulated in sporadic ALS patients. Among these miRNAs, miR-338-3p has already been reported in an earlier study to be deregulated in brains of ALS patients [73]. Thus, miRNA profiles in the peripheral blood leukocytes of sporadic ALS patients may facilitate our understanding of the pathogenesis of ALS or may serve as biomarkers of this disease.

Likewise, miRNA expression profiling was conducted on spinal cord tissue in sporadic ALS and healthy controls. This study also performed functional analysis to find dysregulated miRNAs, which may be contributing to the selective suppression of low molecular weight neurofilament mRNA seen in ALS. Analysis of 664 miRNAs revealed that the majority of those miRNAs were differentially expressed and downregulated in spinal cord tissues of sporadic ALS patients compared to controls. Three miRNAs (miR-146a*, miR-524-5p and miR-582-3p) that are found to be deregulated in sporadic ALS were reported to have the ability to specifically interact with and regulate the neurofilament mRNA 3'-untranslated region, suggesting a role that miRNAs may play in selective suppression of mRNAs in the neurofilamentous aggregate formation in ALS spinal motor neurons [74].

Among the other miRNAs that are emerging as important contributors to ALS pathogenesis is the muscle-specific miR-206, which plays a leading role in muscle development and plasticity [75]. Superoxide dismutase 1 (SOD1) is one of the several genes identified to play a role in the pathogenesis of ALS [76]. When miRNAs were profiled in the muscles of mutant SOD1 mouse model of ALS, a marked increase in miR-206 was noticed in transgenic mice at the onset of symptoms. This increase in miR-206 was found to be a direct result of denervation. Moreover, the loss of miR-206 from transgenic SOD1 mice expedited the rate of disease progression, suggesting that miR-206 is upregulated in cases of nerve injury and it is necessary for regeneration of neuromuscular synapses [77]. Interestingly, a similar increase in miR-206 is also detected in skeletal muscle tissues of human ALS patients compared to healthy controls [78].

DYSREGULATION OF miRNA IN SCHIZOPHRENIA

Schizophrenia is a severe, chronic and disabling mental disorder. Individuals afflicted with this NDD fail to recognize what is real, and display abnormal social behavior. Other symptoms of schizophrenia include auditory hallucinations, delusions, agitated body movements or inactivity for extended periods of time, reduced social interactions and confused thinking. Schizophrenia symptoms begin to surface usually in young adulthood and around 0.3–0.7% of individuals suffer from this disorder sometime during their lifetime [79]. In addition to emotional, behavioral and cognitive problems, individuals suffering from schizophrenia also experience additional psychiatric issues such as anxiety and depression disorder. A substantial proportion of individuals with schizophrenia also suffer from substance abuse disorder [80]. The average life expectancy of persons diagnosed with schizophrenia is about 15 years less than individuals without this disorder, mainly due to higher incidences of suicide rates (as much as 5%) and more frequent health problems

among individuals with this mental disorder [81]. Currently, antipsychotic medicines are the primary treatment for schizophrenia, which may reduce the positive symptoms of psychosis in a week or two. However, antipsychotic medications are not generally able to reduce negative symptoms of psychosis and cognitive impairment associated with schizophrenia [82].

In order to understand the molecular mechanisms underlying the pathological process of schizophrenia, miRNA deregulation has been studied in people with this mental disorder. In one study, the expression of 24 miRNAs was analyzed in the prefrontal cortex (Brodmann's Area 9) from post-mortem brains of 15 schizophrenia patients and 21 healthy, control subjects. As a result, 16 miRNAs were found to be differentially expressed in prefrontal cortex of schizophrenia patients, with 15 of those downregulated. Among those miRNAs, miR26b, miR-29b, miR-30b, and miR106b exhibited a change of almost two fold. More importantly, among the differentially-expressed miRNAs, the ratio of mature miRNA to pre-miRNA was lower in brain tissues of individuals with schizophrenia, providing a clue to impairments of miRNA biosynthesis in NDs such as schizophrenia [83].

In order to study miRNA dysregulation and altered biosynthesis of miRNA in brains of schizophrenia patients, a group of researchers analyzed the expression of 262 miRNAs in postmortem cortical grey matter from the superior temporal gyrus (STG) in a cohort of 21 matched pairs of schizophrenia and non-psychiatric, healthy controls [84]. In a separate study, the same group analyzed the expression of 322 miRNAs in the dorsolateral prefrontal cortex (DL-PFC) as well as STG from the same subjects [85]. Both studies by Beveridge *et al.* reported noticeable upregulation of a significant number of miRNAs in patients with schizophrenia (21% of expressed miRNAs in the STG and 9.5% in the DL-PFC). However, miR-16, miR-20a, miR-128a, and miR-338 were the only four miRNAs out of the 81 dysregulated miRNAs that were found to be upregulated both in the DL-PFC and the STG. It was also revealed in these two studies that the levels of studied miRNAs as well as the miRNA processing enzymes Dicer and DGCR8 were noticeably upregulated in schizophrenia brains, thereby suggesting an increased biogenesis of miRNA within the body.

Strong evidence for changes in miRNA biogenesis comes from studies on one subset of schizophrenic individuals. Hemizygous deletions of the 22q11.2 locus in humans are reported in up to 2% among total population of schizophrenic patients and result in impairments in learning, attention, emotional behavior and functioning [86]. Hence, individuals with 22q11.2 microdeletions are at high risk for developing schizophrenia. Stark *et al.* were able to generate an engineered mouse model with chromosomal deficiency stretching over a segment syntenic to 22q11.2 human locus and noticed many schizophrenia-like phenotypes (such as poor pre-pulse inhibition, enhanced hyperactivity, and lower dendritic spine density) as well as downregulation of mature miRNA levels in the brain [87]. This study also provided evidence that impairment in miRNA biogenesis results due to haploinsufficiency of the *Dgcr8* gene, which plays an important role in the processing of pre-miRNAs to mature miRNAs.

N-methyl-D-aspartic acid (NMDA) is an amino acid that acts as a specific agonist at the NMDA receptors, which are a type of glutamate receptors in the brain playing a pivotal role

in controlling synaptic plasticity and memory function [88]. One recent study analyzed the expression of 854 miRNAs in prefrontal cortical tissues from 100 schizophrenia patients and control subjects and found that miR-132, which is a NMDA-regulated miRNA, was noticeably downregulated in schizophrenia patients [89]. When an NMDA antagonist was administered to adult mice by the same investigators, it resulted in downregulation of miR-132 expression in the prefrontal cortex. It was demonstrated in this study that miR-132 regulates schizophrenia- and neurodevelopment-related genes, including DPYSL3, GATA2, and DNMT3A, strongly suggesting that miRNA and its target genes contribute to abnormal neurodevelopment and pathogenesis of schizophrenia.

DYSREGULATION OF miRNA IN AUTISM

Autism spectrum disorder (ASD) is a highly variable neurodevelopmental disorder characterized by communication difficulties, impairment in social interactions and repetitive, restricted and stereotyped patterns of behavior. The global prevalence of ASD is almost 2 cases per 1,000 children. Boys are four times more likely to suffer from ASD than girls [90]. Autism is most likely a genetic disorder, although it remains unclear as to whether ASD occurs due to rare combinations of common genetic variants or rare mutations themselves [91]. The role of environmental causes such as teratogens, pesticides or nanoparticles is also proposed in the pathogenesis of ASD [92–94]. ASD is a type of NDD because many children with ASD undergo a developmental regression, as evidenced by loss of previously-acquired skills and abilities. Although the exact mechanism is not known, biological processes such as neuronal cell loss, release of proinflammatory cytokines, oxidative stress, and astrocytes and microglial activation have been suggested to contribute to neurodegeneration in ASD [95]. In addition, when changes occur in the way nerve cells and their synapses connect and organize, this ultimately affects the brain's information processing ability, contributing to the pathogenesis of ASD [96]. Currently, there is no known cure for ASD and the commercially available drugs only provide symptomatic relief for ASD.

To the present time, relatively few studies have examined the role of miRNAs in ASD. In one study, 470 mature human miRNAs from six ASD patients and 6 matched controls were assessed for global expression profiling. It was found that 9 of those 470 miRNAs were either upregulated or downregulated in ASD samples compared with controls, suggesting a role for miRNAs in the etiology of ASD [97]. In order to analyze potential transcripts and molecules contributing to ASD pathology, gene and miRNA expression profiling was conducted using cell-line derived total RNA. Compared with controls, numerous dysregulated genes and miRNAs were identified in ASD, including HEY1, SOX9, miR-181b and miR-486, all of which play a critical role in development of the nervous system and function while some of them, like HEY1, are also involved in NOTCH signaling networks [98].

In another study, the expression of miRNAs was analyzed in lymphoblastoid cell lines from monozygotic autistic twins and their unaffected sibling controls using high-throughput miRNA microarray analysis. Results from this study revealed that genes highly involved in neurological functions and disorders as well as genes involved in steroid hormone

metabolism/receptor signaling, gastrointestinal disorders, and circadian rhythm signaling were the targets of differentially expressed miRNAs. Furthermore, two of the reverse transcription polymerase chain reactions confirmed brain-specific miRNAs (miR-29b and miR-219-5p) and their putative gene targets (ID3 and PLK2) were verified by miRNA overexpression or knockdown assays, respectively [99]. ID3 and PLK2 have been linked to circadian rhythm signaling and regulation of synapses, respectively, which are important in ASD [100–102]. It is worthwhile noting that the downregulation of miR-106b and upregulation of miR-23a observed in ASD samples were similar to the findings reported in a previous study by another group of researchers in which they compared and analyzed the expression of 466 human miRNAs from postmortem cerebellum tissue of 13 ASD patients *versus* 13 control, non-autistic cerebellar samples. They found altered miRNA expression levels in cerebellar cortex from ASD patients, suggesting that deregulation of miRNAs may contribute to the pathogenesis of ASD [103]. Among the predicted target genes deregulated by miRNAs present were SHANK3 and Neurexin, which are known genetic causes of ASD [104].

CONCLUSION

Although many advances have been made in our knowledge of the role of miRNAs in regulating gene expression, there are still gaps in our understanding as to how miRNAs specifically contribute to the pathogenesis and progression of NDs. There still exists a need to gain a better understanding as to whether miRNA dysregulation is a downstream consequence or a cause of NDs and whether individual miRNAs are specifically important in a certain NDD or potentially an entire group of miRNAs that collectively serve as a causative factor to cause NDs. We also need to find out which miRNA target or targets are pertinent to a specific NDD. To get a conclusive answer to these questions, it will be important to produce conditional knockout animal models in which developmental defects can be bypassed, making it possible to analyze the functions of specific miRNAs in the human brain [105]. The use of miRNAs as therapeutic targets remains a challenge not only in terms of target specificity but also in regard to their ability to cross the blood-brain barrier to enter the brain in pharmacologically relevant amounts. Development of effective therapies is complicated due to the involvement of multiple signaling pathways in psychiatric disorders and the lack of truly predictive animal models of human disease. Therefore, focusing on the role of miRNAs in psychiatric diseases may shed light on dysregulation of multiple miRNA pathways and may offer opportunity to develop novel treatments that can target entire gene networks [106].

LIST OF ABBREVIATIONS

AD	Alzheimer Disease
ALS	Amyotrophic Lateral Sclerosis
APP	Amyloid Precursor Protein
ASD	Autism Spectrum Disorder

DL-PFC	Dorsolateral Prefrontal Cortex
DNs	Dopaminergic Neurons
HD	Huntington Disease
Htt	Huntingtin Gene
miRNA	MicroRNA
NDs	Neurological Disorders
NFL mRNA	Neurofilament mRNA
NMDA	N-Methyl-D-Aspartic Acid
PD	Parkinson's Disease
SOD1	Superoxide Dismutase 1
STG	Superior Temporal Gyrus

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Table 1

Summary of Dysregulation of microRNAs in Neurological Disorders.

	Names of miRNAs	Type of Dys-Regulation	Sample	Observations/Mechanisms/Implications	Reference(s)
Alzheimer Disease	miR-106a, miR-106b	↓	brains of AD patients	Direct binding to APP mRNA and the subsequent downregulation was seen in the anterior temporal cortex of AD subjects	[32, 33]
	miR-9	↓	primary neuron cultures	<i>In vitro</i> addition of β -amyloid to primary neuron cultures results in a rapid decline in the levels of miR-9, suggesting that plaque formation is associated with deregulation of miR-9	[34]
	miR-9, miR-125b, miR-128	↑	brains of AD patients	Abnormal miRNA-mediated processing of mRNA populations may play a pivotal role in neural impairment observed in AD brain	[35]
	miR-210, miR-9	↓	brains of AD patients	Dysregulated miRNAs in the brains of AD patients can serve as biomarkers for pathways in AD pathogenesis such as neurogenesis, β -amyloid processing and insulin resistance	[36]
	miR-125b	↑			
	miR-107	↓	brains of AD patients	miR-107 has been implicated in accelerating disease progression through regulation of BACE1	[39]
	miR-146a	↑	brains of AD patients	Involved in the processing of APP β -amyloid metabolism; upregulation specifically noted in temporal cortex and hippocampus, known brain areas affected in AD	[42, 43, 45]
Parkinson's Disease	miR-133b	↓ (absent)	brains of PD patients	Completely absent in midbrain tissues of PD patients; miR-133b regulates the maturation and functioning of midbrain dopaminergic neurons through a negative-feedback circuit	[52]
	miR-21*, miR-26b, miR-224, miR-373*, miR-301b, miR-106b	↑	brains of PD patients	In PD brain tissues, those miRNAs target and impair the chaperone-mediated autophagy pathway, hence, disrupting α -synuclein protein degradation and contributing to Lewy body pathology	[57, 58]
	miR-125a-3p, miR-137, miR-181c, miR-193a-3p, miR-196b, miR-331-5p, miR-454	↑	plasma of PD patients	May serve as effective PD biomarkers in the plasma of PD patients	[60]
	miR-1, miR-22*, miR-29a	↓	blood of PD patients	May serve as effective PD biomarkers in the blood of PD patients	[59]
Huntington's Disease	miR-34b	↑	plasma of HD gene carrier individuals	miR-34b may serve as a potential biomarker of HD prior to the onset of disease symptoms	[66]
	miR-200a, miR-200c	↑	brains of mutant HD mice	Differential expression of miR-200a and miR-200c may interrupt the biogenesis of proteins involved in synaptic plasticity and neuronal survival	[67]

	Names of miRNAs	Type of Dys-Regulation	Sample	Observations/Mechanisms/Implications	Reference(s)
	miR-125b, miR-146a, and miR-150	↓	<i>in vitro</i> cell-based assays	These miRNAs target Htt and modulate Htt aggregate formation by interacting with tata binding protein	[68]
Amyotrophic Lateral Sclerosis	miR-149, miR-328, miR-338-3p, miR-451, miR-583, miR-638, miR-665, miR-1275	↑ ↓	peripheral blood leukocytes of ALS patients	May serve as biomarkers for ALS	[72, 73]
	miR-146a*, miR-524-5p, miR-582-3p	↓	spinal cord tissue of ALS patients	Have ability to specifically interact with and regulate the neurofilament mRNA 3'-untranslated region, hence playing a key role in selective suppression of mRNAs in the neurofilamentous aggregate formation in ALS spinal motor neurons	[74]
	miR-206	↑	skeletal muscle tissues of ALS patients	This muscle-specific miRNA plays a leading role in muscle development and plasticity; dysregulation may contribute to ALS pathogenesis	[75, 77, 78]
	miR26b, miR-29b, miR-30b, miR106b	↓	brains of schizophrenia patients	The expression of these miRNAs in the prefrontal cortex of Schizophrenia patients exhibited two fold downregulation; the ratio of mature miRNA to pri-miRNA was lower in brain tissues of individuals with schizophrenia	[83]
Schizophrenia	miR-16, miR-20a, miR-128a, miR-338	↑	brains of Schizophrenia patients	These four miRNAs were found to be upregulated both in the DL-PFC and the STG in schizophrenia brains, suggesting an increased biogenesis of miRNA in the body	[84, 85]
	miR-132	↓	brains of schizophrenia patients	Regulates schizophrenia- and neurodevelopment-related genes	[89]
	miR-132, miR-146a, miR-146b, miR-23a, miR-23b, miR-663	↑	lymphoblastoid cell lines from autism patients	This study demonstrated the feasibility of examining lymphoblastoid cell lines to study the role of microRNAs in autism	[97]
Autism	miR-92 (a1-a2), miR-320, miR-363	↓	lymphoblastoid cell lines from autism patients	Plays a critical role in development of nervous system and function by targeting SFRS3 gene (a gene involved in memory formation)	[98]
	miR-486	↑ ↓	lymphoblastoid cell lines from autism patients	For these two brain-specific miRNAs, their putative genes (ID3 and PLK2) were verified by miRNA overexpression or knockdown assays; ID3 and PLK2 have been linked to circadian rhythm signaling and regulation of synapses, respectively.	[99–102]
	miR-29b	↑	lymphoblastoid cell lines from monozygotic autistic twins	Altered miRNA expression levels observed in postmortem cerebellar cortex from ASD patients, implicating the role of miRNA dysregulation in the development of ASD	[103]
	miR-219-5p	↓			
	miR-106b	↓	brains of ASD patients		
	miR-23a	↑			

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List of Abbreviations: Downregulated (↓); Upregulated (↑); Differentially Regulated (↑ ↓); Amyloid Precursor Protein (APP), Autism Spectrum Disorder (ASD), Beta-Site Amyloid Precursor Protein-Cleaving Enzyme 1 (BACE1), Dorsolateral Prefrontal Cortex (DL-PFC), Huntington Gene (Htt), Huntington Disease (HD), MicroRNA (miRNA), MessengerRNA (mRNA), Parkinson's Disease (PD), Superior Temporal Gyrus (STG).