Roles of miRNAs in Neurodegenerative Diseases

Subjects: Biology

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There are many types of neurodegenerative diseases, and the most common ones are Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). AD is a neuron-centered disease generally characterized by Aβ and tau phosphorylation. PD is generally characterized by progressive deterioration of motor function due to loss of nigrostriatal dopaminergic neurons with muscle rigidity, bradykinesia and resting tremor. ALS is a fatal onset disease characterized by selective loss of upper and lower motor neurons. HD is a predominantly genetic disease, for which there is no drug cure and it is ultimately fatal. Although their underlying mechanisms remain elusive, many studies have revealed that a series of miRNAs are involved in the development of these diseases. MiRNA regulation happens prior to neurological damage, which emphasizes the significance of miRNA alterations in the disease development. Upregulation/downregulation of miRNA expression leads to the alteration of the protein expressed by the corresponding pathogenic gene, which ultimately results in occurrence and development of neurodegenerative diseases.

neurodegenerative diseases microRNA early diagnosis

1. miRNA in Alzheimer's Disease (AD)

AD is the most common neurodegenerative disease that often occurs in people over the age of 65 and affects cognition, memory, language and behavior. It affects around 40 to 50 million people worldwide, but the number of cases is expected to triple by 2050 due to population growth and aging [1]. Although many efforts have been made in the past few decades, the complex pathogenesis of the disease remains unclarified, which limits the development of both diagnosis and treatment methods [2][3][4][5]. The potential of miRNA as biomarkers for early diagnosis of AD has attracted much attention as more and more miRNAs have been found altered in various processes implicated in AD. AD is characterized by two landmarks, the overproduction of Aβ and hyperphosphorylation of tau protein (**Figure 1**). Moreover, both oxidative stress and neuroinflammation have been reported to contribute to the development of AD [6]. Quite a lot of miRNAs has been reported to be implicated in these processes during AD development. MiR-132, known as "NeurimmiR" due to its involvement in numerous neurophysiological and pathological processes, was identified to be involved in Aβ and tau pathology [7]. Another study showed a few miRNAs such as miR-592, miR-125b and miR-144 were dysregulated, which were associated with AD by regulating oxidative stress [8]. Similarly, a number of miRNAs including miR-155 and miR-146a were investigated and are believed to contribute to the process of neuroinflammation in AD [9].

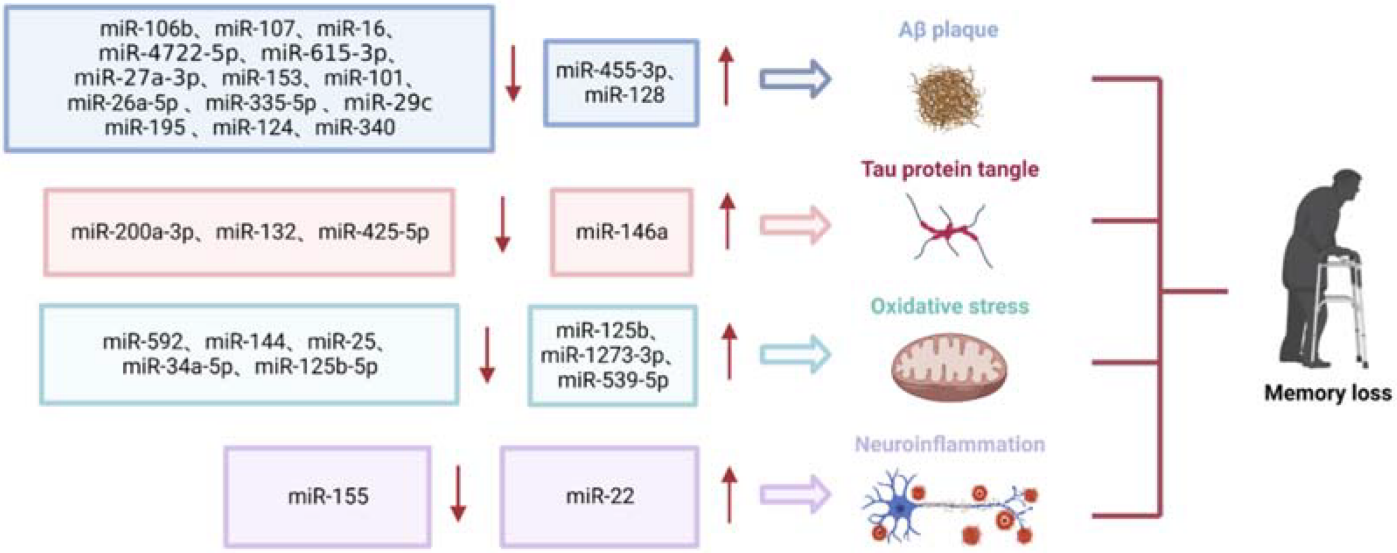

Figure 1. MiRNAs abnormally expressed miRNAs in AD.

1.1. Role of miRNAs in Aβ Deposition

In AD, the dysregulation of the Aβ level leads to the appearance of senile plaques which contain Aβ depositions. Aβ is a complex biological molecule which interacts with many types of receptors and/or forms insoluble assemblies [10][11]. Aβ is generated by sequential cleavages of amyloid precursor protein (APP) by beta-site APP cleaving enzyme 1 (BACE1) and γ-secretases [12][13]. Its non-physiological depositions alternate with the normal neuronal conditions, impairing synaptic activity and inducing neuritis as well as triggering neurodegeneration. Thus, the role of Aβ deposition in AD has been extensively studied, including the miRNAs involved in this process. For instance, blood samples were collected from 33 AD patients and 33 healthy controls for experiments, and the mRNA expression levels of miR-4722-5p and miR-615-3p were up-regulated in AD [14]. Another study collected serum and cerebrospinal fluid (CSF) samples from 66 AD patients, and the expression levels of miR-27a-3p and NEAT1 in serum and CSF were measured by real-time quantitative PCR experiments. It was concluded that decreased miR-27a-3p levels and increased NEAT1 levels lead to Aβ deposition [15]. To clarify the underlying pathogenesis, both SH-SY5Y cells and rats were treated with amyloid protein and then miR-27a-3p [15]. Results suggest that amyloid protein triggered upregulated NETA1 and downregulated miR-27a-3p and that these effects were improved by miR-27a-3p compensation [15]. The role of NETA1 was further clarified by another two groups and confirmed that NETA1 could sponge-bind miR-107 and miR-24, promote Aβ deposition, and aggravate Aβ-induced neuronal damage [16][17]. By investigating the expression levels of miR-106b in AD patients, experimental studies showed that miR-106b was significantly downregulated in AD [18]. Down-regulation of miR-106b led to an increase in Aβ levels, which might be due to increased expression of BACE1, thereby driving the shift of APP to the Aβ hydrolysis pathway and promoting Aβ deposition [13]. In clinical and mouse model studies, miR-106b expression can be regulated by simvastatin to improve the symptoms of AD [19]. Reduced expression of miR-107 in early AD patients might enable Aβ deposition through regulation of BACE1 [20][21]. In a mouse model of AD, some drugs improved memory loss and reduced Aβ deposition in mice [22]. MiR-29c [23], miR-195 [24], and miR-124 [25] were

demonstrated to inhibit the expression of BACE1 by binding with the 3 ‘-UTRs of BACE1. As the levels of these miRNAs decreased in AD, the levels of Aβ increased. The down-regulated expression of miR-16 [10][26], miR-153 [27] and miR-101 [28], which all bind to the 3′-UTRs of *APP*, resulted in an increase in the transcription and protein expression of *APP* and a further increase in the production of Aβ. Another study showed that the expression profile of miR-455-3p was significantly upregulated in AD patients compared to the healthy group [29]. In transgenic AD mice, the expression of miR-26a-5p was reduced, which could be regulated by DYRK1A and overexpression of miR-26a-5p was able to inhibit Aβ deposition [30]. Similarly, in transgenic mice and SH-SY5Y cells, overexpression of miR-335-5p significantly decreased protein levels of Aβ in cells and reduced apoptosis, while inhibition of miR-335-5p produced the opposite result. Furthermore, overexpression of miR-335-5p significantly improved cognitive performance in transgenic mice [31]. MiR-340 was downregulated in AD mice and reduced Aβ accumulation by targeting BACE1 [32]. MiR-128 was upregulated in the cerebral cortex of AD mice and knockout miR-128 suppressed symptoms and reduced Aβ production in AD mice [33]. Therefore, a considerable number of miRNAs play roles in Aβ deposition.

1.2. Role of miRNAs in Tau Phosphorylation

Elevated phosphorylation and aggregation of tau protein are widely considered pathological hallmarks of AD [34]. The microtubule-associated tau protein contributes to the stability of axonal microtubules in the brain and is involved in the regulation of axon outgrowth and axonal transport. The binding of tau to microtubules is regulated by post-translational modifications, mostly phosphorylation, which also controls various other less characterized functions of tau [35]. Moreover, tau protein is an important component of neurofibrillary tangles, affecting mitochondrial respiration and synaptic information transmission in neurons [36]. However, the underlying mechanisms remain elusive, which limits the development of effective diagnosing and treatment methods in terms of tau phosphorylation. MiRNAs stand out as potential biomarkers contributing to clarifying the pathogenesis. In animal and cellular models of AD, the expression of miR-200a-3p was suppressed, and miR-200a-3p treatment inhibited apoptosis, inactivated Bax/caspase-3 axis and phosphorylated tau protein [37]. Mechanistically, these effects were mediated by regulating the transport of BACE1 and PRKACB [38]. In detail, the neuroprotective effect of miR-200a-3p was achieved through inhibition of BACE1 expression and subsequent inhibition of Aβ production and reduction of PKA expression and tau phosphorylation [37]. Quite a lot of studies have confirmed downregulation of miR-132 in AD and proposed that miR-132 is involved in AD by controlling apoptosis and tau phosphorylation [39][40][41][42]. Meanwhile, miR-132 expression was shown to be reduced in AD-derived plasma exosomes [39]. Moreover, it was shown that over-expressed miR-425-5p induced apoptosis and promoted tau phosphorylation by targeting the HSPB8 fraction in AD [43]. MiR-146a was also upregulated in AD, and miR-146a adjustment was shown to improve cognitive impairment and alleviate the entire pathological processes, including tau phosphorylation, in *APP/PS1* transgenic mice, a mouse model of AD [44]. Collectively, a series of miRNAs are tightly associated with tau phosphorylation.

1.3. Role of miRNAs in Oxidative Stress

Oxidative stress could activate microglia and astrocytes, leading to Ca^{2+} influx and mitochondrial damage in synapses, followed by AD [45]. Oxidative stress is caused by an imbalanced redox state, including overproduction of reactive oxygen species (ROS) or dysfunction of the antioxidant system [46]. The brain is one of the organs particularly vulnerable to ROS because of its high oxygen demand and abundance of peroxidizable fat cells [46]. Physiological changes in these cells may lead to a variety of pathological conditions and human diseases, especially AD [47]. According to numerous studies, oxidative stress has been considered important for the development of AD because it can cause chronic inflammation in the early stages of neurodegeneration, leading to mitochondrial dysfunction, oxidative damage to nucleic acids, changes in gene expression, and abnormal modification of lipids and proteins [6][46][47][48]. A group of miRNAs have been proposed to contribute to these processes. It was indicated that miR-125b induced oxidative stress by inducing Aβ peptide production and sphingosine kinase 1 suppression in an in vitro model of AD [49]. Other studies showed miR-592 and miR-144 modulated oxidative stress by targeting nuclear factor erythroid 2-related factor 2 (Nrf2) in primary astrocytes and SH-SY5Y cells, respectively [50][51]. Similarly, miR-25 affected a form of Aβ-induced oxidative stress by downregulating Nrf2, leading to apoptosis induction [52]. In AD models, overexpression of miR-1273g-3p and miR-539-5p induced oxidative stress, ultimately leading to Aβ production [53][54]. MiR-34a-5p and miR-125b-5p reduced oxidative stress by targeting BACE1, inhibited Aβ-induced neurotoxicity, and provided new targets for AD [55].

1.4. Role of miRNAs in Neuroinflammation

Neuroinflammation is also an important factor in the pathogenesis of AD [56]. Neuroinflammation is generally defined as an inflammatory response in the central nervous system (CNS) that is caused by trauma, ischemia, infection and other pathological injuries such as toxin accumulation [57]. According to research reports, AD is associated with neuroinflammatory responses, including enhanced astrocyte reactivity, microglia activity, and increased chemokine and inflammatory cytokine loads, which are together believed to promote neurodegeneration [58]. Neuroinflammation is considered to be an important driver in AD, which is generally a chronic process that does not resolve on its own and is associated with the blood-brain barrier and multiple pro-inflammatory factors. There have also been many studies suggesting that AD was closely related to immune mechanisms, which were briefly described here [59][60][61]. In detail, elevated levels of proteins associated with AD pathology and disease severity in AD were positively correlated because these proteins could stimulate receptors on astrocytes and microglia to trigger immune responses, which led to the release of inflammatory mediators [62][63][64]. Another study showed that miR-155 activated astrocytes and led to the production of several pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) [65]. Activation of inflammasomes in the context of neuroinflammation ultimately led to focal chain cell death by regulating secretion of pro-inflammatory cytokines and cleavage of the N-terminal end of gasdermin D (GSDMD) [66][67]. It was shown that miR-22 expression was reduced in AD patients, and complementation of miR-22 in *APP/PS1* mouse model was able to significantly improve memory and behavior and inhibit the expression of pro-inflammatory cytokines such as IL-1β and IL-1 by suppressing GSDMD [68]. Based on these findings, miRNAs could be considered to play an early diagnostic role in the control of neuroinflammation. Thus, miRNAs could be used as an option for early diagnosis of neurodegenerative diseases.

2. miRNA in Parkinson's Disease (PD)

PD is the second most common neurodegenerative disease in neurology after AD. The dopaminergic neurons of the midbrain nigrostriatal gradually lose their function and accumulate to a certain extent before the onset of the disease, manifesting as movement disorders and even developing into dementia [69]. It displays as the degeneration and death of dopamine neurons in the brain and causes dementia and mental illness as the symptoms spread to other areas of the brain. Its pathological feature is the formation of a Louis body, which is mainly formed by the aggregation of α-synuclein [70]. A series of miRNAs have been proved to be involved in the pathological processes of PD, such as overexpression of α-synuclein and LRRK2 dysregulation [71]. For instance, Briggs and co-workers showed that miR-744 and miR-532-5p were downregulated, while miR-132, miR-92a, miR-27a and miR-148a were upregulated in brain samples of PD patients [72]. MiRNA can regulate the pathological process of PD through the post-transcriptional expression of α-synuclein and LRRK2, which has become a new tool for the early diagnosis of PD.

Mutations in the α-synuclein gene, which encodes the α-synuclein protein, are known to be one of the main hallmarks of PD [73][74][75]. α-Synuclein are located at the synaptic terminal and widely exist in the adult brain, especially in the neocortex and hippocampus [76]. Overproduced α-synuclein were aggregated to form Lewy bodies, leading to the death of dopaminergic neurons, which in turn triggers PD [77]. Therefore, reducing the expression of α-synuclein through pharmacological intervention might alleviate PD symptoms. A large number of studies have shown that many miRNAs could affect the expression of α-synuclein, some of which have been reported in PD patients [78][79][80]. The most significant miRNAs in α-synuclein expression were probably miR-7 and miR-153 [81]. These two miRNAs reduced α-synuclein levels in PD mice through different pathways, with miR-7 inhibiting its translation and miR-153 degrading mRNA [81][82]. These suggested that they might have a neuroprotective effect in PD patients. In PD patients, miR-7 expression was significantly reduced [83]. It was shown that overexpression of miR-153 and miR-7 in human embryonic kidney cell lines HEK293 cells and cortical neurons led to a significant reduction in α-synuclein mRNA and protein expression levels, while miR-7 knockdown induced overexpression of α-synuclein protein levels [81][83]. Other miRNAs identified as regulators of α-synuclein expression include miR-30b, miR-34b/c, miR-214 and miR-433 [84][85][86].

LRRK2 is a member of the leucine-rich repeat protein kinase family, involved in early neurodevelopmental processes, and its acquired mutations cause familial and sporadic PD [87]. LRRK2 interacts with the miRNA pathway to regulate protein synthesis. LRRK2 mutations result in dopaminergic neuronal degeneration and apoptosis via enhancing LRRK2 kinase activity [88]. LRRK2 mutation could also reduce the expression of miRNAs, because LRRK2 mutation affected the two components argonaute-1 and argonaute-2 in RNA-induced silencing complex, which regulate miRNA functions [89]. MiR-205 was down-regulated in the brain tissue of PD patients, and three transcription factors of the LRRK2 gene were inhibited, resulting in a negative correlation between the expression of LRRK2 protein and the expression of miR-205 [90]. In HEK293T cells, overexpression of miR-205 was involved in inhibiting the expression of LRRK2 protein, whereas inhibiting overexpression of miR-205 enhanced the expression of LRRK2 protein [90]. Overexpression of miR-599 inhibited LRRK2 expression, and

downregulation of miR-599 protected SH-SY5Y cells from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced apoptosis [91].

3. miRNA in Amyotrophic Lateral Sclerosis (ALS)

ALS is a fatal neurodegenerative disease with a mean incidence of 1.8/100,000 and a mean prevalence of 3.40/100,000 in North America [92]. It is characterized by progressive loss of upper and lower motor neurons in the spinal cord, cerebral cortex, and brainstem, resulting in muscle weakness and atrophy, and ultimately paralysis [93]. The pathogenic mechanisms of ALS are poorly understood, although a percentage of patients have familial disease or mutations in genes that are closely related to neuronal function [94][95]. The expression profile of miRNAs stands out as a novel direction for the diagnosis and treatment of the disease [96]. To prove that altered expression of miRNAs is an important factor in ALS disease progression, a recent comprehensive analysis revealed that at least 40 miRNAs were differentially expressed in the muscle tissue of ALS subjects [97].

With the deepening of the understanding of miRNAs, studies have found that miRNAs are involved in the regulatory process of ALS [98][99]. In ALS mice, miR-206 was found to be abundantly produced, and its upregulation was consistent with the resulting disorder. It was verified by relevant experiments that the lack of expression of miR-206 can slow down the pathological process of ALS and prolong its lifespan [100]. In ALS, another widely studied miRNA is miR-155. The increase of miR-155 in the brain was a detrimental factor for ALS, as the survival rate of rats was increased when miR-155 expression in ALS model mouse brain was inhibited [101]. This suggested that miR-155 has the potential to be a target for the diagnosis of ALS. In the spinal cord of ALS patients, down-regulation of miR-9 and miR-105 targeted the 3'-UTRs of the three intermediate filaments of INA, NEFL and PRPH to regulate gene expression [102]. Therefore, downregulation of these two miRNAs may lead to an imbalance of intermediate filaments, which in turn slows the progression of ALS. Therefore, miRNAs may be a potential strategy for early diagnosis and treatment of ALS.

4. miRNA in Huntington's Disease (HD)

HD, as one of the common neurodegenerative diseases, is a genetic and relatively rare disease that is characterized by progressive motor dysfunction, neurocognitive degeneration and brain atrophy [103]. HD is a monogenic disease and the causative gene is *Huntingtin* (*HTT*). Patients carrying mutant *HTT* (*mHTT*) with more than 36 CAG repeats in the exon 1 region of *HTT* will gradually develop HD symptoms [104][105][106][107][108][109][110] (**Figure 2**). The typical characteristics of HD neuropathology include intranuclear inclusions, nuclear aggregates and neuropil aggregates. The cause of death usually is suicide, as HD patients are unable to tolerate the painful conditions of the symptoms [111][112]. However, except for the symptomatic treatment for motor and psychiatric symptoms, there is no effective treatment for this disease. In recent years, the role of miRNA imbalance in neurological disorders has received increasing attention from researchers in search of new diagnostic approaches and treatment strategies. Several studies have reported the expression profile of miRNAs in HD patients, and altered miRNAs were highly correlated with the regulation of molecular or pathological phenotypes [106][113][114][115]

[116][117][118][119][120]. Thus, in recent years, aberrant miRNA expression has been reported in HD patients, in vitro experimental models and transgenic HD animal models [114][120][121]. In the near future, dysregulation of miRNAs is likely to be useful for early diagnosis of HD.

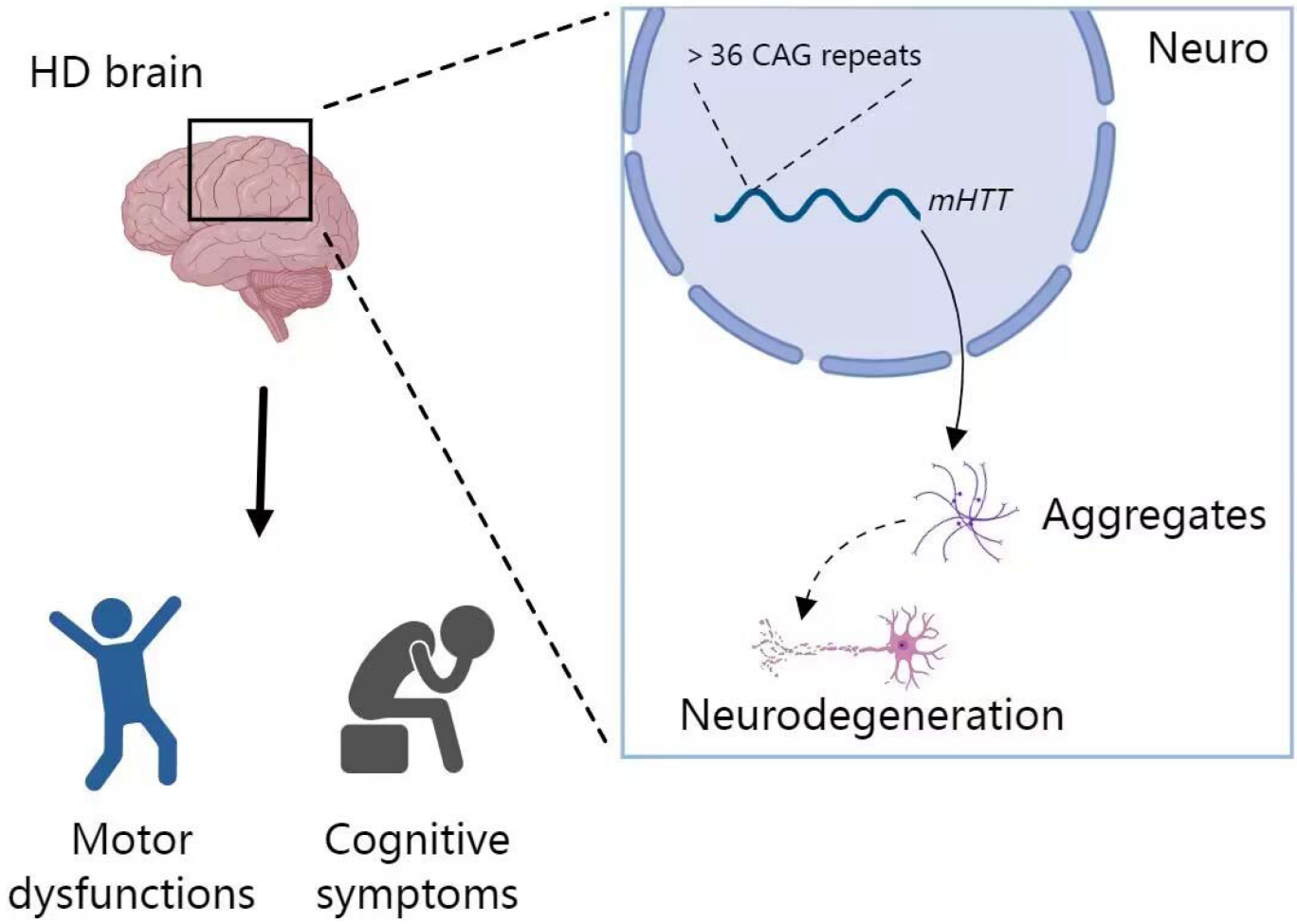

Figure 2. Schematic representation of HD pathogenesis.

An increasing number of studies have shown that miRNAs were dysregulated in HD [122][123][124]. Reed et al. detected a total of 2081 miRNAs by diagnosing HD patients and normal groups, of which miR-520f-3p, miR-135b-3p, miR-4317, miR-3928-5p, miR-8082, miR-140-5p and other miRNAs were expressed at significantly higher levels in HD patients [114]. The expression of two miRNAs, miR-124a and miR-132, was found to be decreased in transgenic HD mice, which was attributed to the abnormal REST leading to increased levels of the target mRNAs of these two miRNAs, further leading to abnormal expression of miR-124a and miR-132 [125]. The expression level of miR-9 was found to be reduced in the cortex of HD patients compared to the normal group, which was also due to the abnormal REST [126]. These studies suggest that miRNAs are extensively involved in the pathogenesis of HD by regulating the target gene *REST*. Due to the limited manipulation of miRNA alterations in HD patients, miRNA studies have been extensively investigated and validated in different animal models. The study reported that miR-128a was downregulated in transgenic HD monkeys, and also confirmed that miR-128a was also

downregulated in the brains of pre-symptomatic and post-symptomatic HD patients, suggesting that transgenic HD monkeys and HD patients may exhibit some similar profiles of miRNAs [103]. Similarly, in transgenic mouse studies, miR-34a, miR-124 and miR-132 were suppressed in expression in mouse models, which is similar to HD patients [123][127].

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