Neuroprotection of microRNA in neurological disorders (Review)

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Abstract. MicroRNAs (miRNAs) are small, endogenous, non-coding RNA molecules that function as post-transcriptional regulators of gene expression by imperfect base-pairing with the 3'-untranslated regions of their target mRNAs. Altered expression of numerous miRNAs has been shown to be extensively involved in the pathogenesis of various diseases and cancers. Additionally, the specific expression of miRNAs in the nervous system has indicated that miRNAs are critical for the occurrence and development of neurological diseases. Increasing evidence has shown that specific miRNAs target the expression of particular proteins that are significant in the disease pathogenesis. Therefore, miRNA-mediated regulation may be important in the occurrence and development of neurological diseases and may function as a novel biomarker and tool for clinical therapy. In the present study, the significance of miRNAs is reviewed in a number of neurological disorders and the possibility of their use in therapeutic interventions is evaluated.

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1. Introduction

MicroRNAs (miRNAs) are small, endogenous, non-coding RNA molecules that generally contain 19-24 nucleotides (nt), which are cleaved from a 70-80-nt partially duplexed precursor (pre-miRNA). miRNAs usually regulate gene expression at a post-transcriptional level through imperfect pairing with the 3'-untranslated regions (3'-UTR) of target mRNAs, and can therefore modulate diverse biological processes, including cell differentiation, cell cycle, proliferation, apoptosis and cellular response to stress (1-3). The abnormal expression of miRNAs has been proven to be extensively involved in the pathogenesis of numerous types of diseases and cancers, including lung cancer (4), gastric cancer (5), cardiovascular disease (6), breast cancer (7), hepatocellular carcinoma (8) and lymphocytic leukemia (9). Therefore, miRNA may play important roles in the occurrence and development of various types of cancer and may function as a novel biomarker and tool for clinical therapy.

miRNAs have also been shown to play critical roles in the development and function of the brain. Several miRNAs (miR-9, miR-124a/b, miR-135, miR-153, miR-183 and miR-219) were found to be specifically expressed in differentiating neurons, which suggests that these miRNAs act as effectors in neuronal processes (10). Furthermore, it has been previously demonstrated that miRNAs evidently have tissue-specific expression (11). One example is the significantly higher expression of let-7g, miR-92b, miR-146b, miR-330*, miR-384 and miR-551b in the rat hippocampus compared to the cortex (12). By contrast, miR-15b, miR-16, miR-204 and miR-221 are clearly abundant in the axons of superior cervical ganglia neurons (13). The results from those studies suggested that miRNAs may play important roles in the brain at a sub-cellular level.

Thus far, an increasing number of miRNAs have been proven to be critical for the pathogenesis of neurological diseases (14,15). The finding of miRNAs has expanded the potential for diagnostic markers and therapeutic targets for human diseases, including neurological diseases. In the present review, the neuroprotective roles of miRNAs in cerebral ischemia, stroke, epilepsy and traumatic injury have been evaluated. In addition, the increasing attention that has been administered to miRNAs in association with neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), was addressed.

2. Cerebral ischemia

Brain ischemia is one of the most universal reasons for disability and mortality worldwide. Ischemic preconditioning (IP) triggers a temporal change of gene expression in the cerebral and a concomitant altered expression of proteins that protect the brain during a subsequent ischemic injury (16,17).

An increasing number of studies have revealed that the miRNA profiles alter following cerebral ischemia, inferring that miRNAs may be involved in the pathogenesis of cerebral ischemia (Table I). A study by Dharap and Vemuganti (18) found that miRNAs react rapidly in the cerebral cortex of rats subjected to IP. The expression of 20 miRNAs were altered from 6 h to 3 days after pre-conditioning (PC), in which approximately nine miRNAs showed a clear change. Lee *et al* (19) proved that the miR-200 (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) and miR-182 families (miR-182, miR-183 and miR-96) are upregulated 3 h after early IP. In addition, miR-19 and miR-681 are upregulated and miR-468 is downregulated 24 h after IP. A study by Lusardi *et al* (20) detected the miRNA expression in the mouse cortex in response to IP, ischemic injury and tolerance. The 273, 144 and 50 miRNAs were found to be significantly altered in preconditioned, ischemic and tolerant cortex, respectively. Dharap *et al* (21) also reported the miRNAs profile at the reperfusion time point following transient middle cerebral artery occlusion in an adult rat brain. There was an increase of three miRNAs and a decrease of eight following 3 h of reperfusion. Additionally, the number of abnormal miRNAs gradually increased as the reperfusion time progressed. Subsequent to 3 days of reperfusion, 24 miRNAs were found to be notably increased and 22 decreased. A total of 12 miRNAs were decreased and eight increased at 4 of 5 time points between 3 h and 3 days of reperfusion. In particular, the expression of miR-290 increased by 63-fold following 3 days of reperfusion, and miR-153 was shown to decrease by 52-fold after 1 day of reperfusion. The aforementioned results indicated that miRNAs may play important roles in cerebral ischemia and reperfusion. Therefore, further elucidation of miRNAs is useful for understanding the pathogenesis of cerebral ischemia and devising novel strategies for its therapy.

Although the precise mechanism of miRNAs as regulators is not fully understood, it has been proven that miRNAs exert irreplaceable roles by controlling the levels of various target mRNAs and functional proteins, which are important for preserving the function of tissues or cells (1). In an adult rat brain of transient focal ischemia, aberrant miRNAs are predicted to target proteins that are involved in mediating numerous functions, including transcription, inflammation, neuroprotection and ionic homeostasis (Table II). For example, miR-497 is specifically induced following transient ischemia. A loss of miR-497 has also been proven to suppress cell death, whereas overexpression increases neuronal loss (22). A direct target of miR-497 is B-cell lymphoma (Bcl)-2/-w, which attenuated brain infarction and improved the neurological outcome following focal ischemia. The knockdown of miR-497 enhances the Bcl-2/-w expression, showing that miR-497 exerts the role of apoptosis by repressing Bcl-2/-w in the pathogenesis of ischemic brain injury (22). Lusardi *et al* (20) revealed that miR-132 directly regulates methyl-CpG binding

protein 2 (MeCP$_2$) protein expression that acts as an effector of IP-induced tolerance in rat cortical neurons. Lee *et al* (19) found that the miR-200 family decreased the expression of prolyl hydroxylase 2 (PHD2), but increased the levels of hypoxia-inducible factor 1 (HIF-1) in Neuro-2a cells, suggesting that the miR-200 family have a neuroprotective effect by mainly reducing PHD2 as a post-translational regulator of HIF during hypoxia. miR-29c, a pro-survival miRNA, decreases the post-ischemic infarct volume through targeting DNA methyltransferase 3a (DNMT3a). Furthermore, transcription factor REST has been shown to be an upstream transcriptional regulator of miR-29c (23). The knockdown of REST prevents miR-29c downregulation and DNMT3a induction, and reduces ischemic cell death. Following 3-nitropropionic acid preconditioning in rat brain, miR-199a expression is significantly reduced in the hippocampus on the 2nd day (24). Sirt1, a putative target of miR-199a and a neuroprotective mediator in brain ischemic tolerance, is significantly upregulated following the knockdown of miR-199a. Therefore, it is hypothesized that miR-199a may play a role in cerebral ischemic tolerance by targeting Sirt1. As a single miRNA can target hundreds of proteins and a target is regulated by several miRNAs (25), it is extremely possible that multiple proteins are involved in the physiology of IP and reperfusion simultaneously.

It is known that miRNA simultaneously regulates the activities of several pathways by focusing on numerous target mRNAs concomitantly (26). The predicted targets of altered miRNAs have been proven to be involved in inflammation, apoptosis and neuronal repair. During the pathogenesis of IP, mRNAs have also been found to be closely linked with a number of signaling pathways. Dharap and Vemuganti (18) detected the abnormal expression of miRNAs in the cerebral cortex of rats following PC. The results of that study showed that the upregulated targets of miRNAs are involved in mitogen-activated protein (MAP)-kinase signaling, mammalian target of rapamycin (mTOR) signaling, transforming growth factor (TGF)-β signaling, wingless-type MMTV integration site (Wnt) signaling, v-erb-b2 avian erythroblastic leukemia viral oncogene homolog (ErbB) signaling, gonadotropin-releasing hormone (GnRH) signaling, p53 signaling, insulin signaling, Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling, and Notch signaling. The downregulated targets are the components of Wnt, GnRH, MAP-kinase, TGF-β, ErbB, PI and p53 signaling (18). Additionally, miR-146 regulates the toll-like receptor pathways and nuclear factor-κB-dependent inflammatory responses by targeting the 3'-UTR of TRAF-6 and IRAK-1. miR-199a-3p targets IκB kinase β, MET and extracellular-signal-regulated kinase (ERK)-2, thereby controlling inflammation and ERK-MAPK signaling, which has been proven to participate in injury following ischemia-reperfusion injury (IRI) (27).

miRNAs have also been found to participate in the regulation of certain chemical drugs that have been proven to exhibit neuroprotection in cerebral ischemia. Sevoflurane may induce the significant expression of ischemia-induced miR-15b that subsequently exerts neuroprotective effects by regulating its target proteins, including Bcl-2 (28). miR-203 has been proven to be involved in isoflurane preconditioning-induced neuroprotection by regulating the expression of protein kinase

Table I. Summary of dysregulated miRNAs in neurological diseases in the present review.

Disease	Regulation	Abnormal miRNAs
Cerebral ischemia	Upregulated	let-7a, miR-15b, -19, -21, -26b, -96, -98, -141, -145, -146, 146a, 181b/d, -182 -183, -200a/b/c, -203, -206, -290, -335, -340-5p, -352, -374, -379*,-429, -681
	Downregulated	let-7d*, miR-27a, -29c, -30c-2*, -92b, -132, -137, -199a, -218, -292-5p, -322*, -328, -345-5p, -466c, -468, -494, -497, -873
Stroke	Upregulated	let-7e/f, miR-1, -21, -23a (female), -25*, -26a, -34a, -125b, -145, -181, -181a, -513a-5p, -550, -602, -665, -891a, -923, -933, -939, -1184, -1246, -1261, -1275, -1285, -1290
	Downregulated	miR-15b, -23a (male), -25*, -34b, -124a, -126, -142-3p, -186, -210, -223, -483-5p, -498, -768-5p, -519e, -1259
AD	Upregulated	miR-146a, -197, -320, -423, -511
	Downregulated	let-7i, -9, -15a, -19b, -22, 26b, 29a/b-1, -30a-5p, -93, -98, -101, 106b, -107, -181c, -210, -363
PD	Upregulated	miR-1, -22*.
	Downregulated	miR-7, -15b, -16-2*, -19b, -26a/a2*, -28-5p, -29, -30a/b/c, -34b/c, 29b/c, -101-1 -107, -126, -126*, -133b, -147, -151-3p, -151-5p, -153, -199a-3p, -199a-5p , -218-2, -301a, -335, -345, -374a/b
HD	Upregulated	-
	Downregulated	miR-9/9*, -22, -29c, -124a, -128, -138, -132, -218, -222, -344, -674*
Epilepsy	Upregulated	miR-21, -23a, -27a, -31, -33, -34a,-124, -132 -134, 146a, -152, -203, -210, -211
	Downregulated	miR-19a, -135b, -136, -138*, -144, -153, -190, -221, -222, 296*, -301a, -325-5p, -380, -542-3p, -542-5p, -543
Traumatic injury	Upregulated	miR-20a, -21, -23a, -153, -200a/b, -381, -429, -486, -499, -873
	Downregulated	miR- 19a/b, -31, -135a/b, -136, -144, -148-5p, -222, -296*, -341, -342-5p, -540, -598-5p, -708

miRNA, microRNA; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease.

phospho-Akt, which may promote cell survival (29). A study by Hu *et al* (27) demonstrated the protective role of atorvastatin on IRI and its miRNA-related mechanisms. Thirteen miRNAs were detected and shown to be significantly varied following atorvastatin pretreatment. Of these, six miRNAs were upregulated with changes >2-fold, whereas one miRNA was downregulated with a 3.4-fold change. miRNAs activated and repressed translation in the course of cerebral ischemia by modulating a number of target proteins of differential signaling pathways. Findings of the aforementioned studies may improve the understanding of the mechanisms underlying cerebral ischemia.

3. Stroke

Stroke is an important cause of mortality and morbidity worldwide. Previous studies have shown that stroke also induces changes in the miRNA expression profiles in rodents, as well as humans (30,31) (Table I).

Tan *et al* (29) carried out miRNA profiling using peripheral blood obtained from young stroke patients, aged 18-49 years. In total, 138 miRNAs were highly expressed and 19 miRNAs were poorly expressed in stroke patients. Another eight miRNAs (hsa-let-7f, miR-126, -1259, -142-3p, -15b, -186, -519e and -768-5p) were also poorly expressed in the three subtypes of stroke (large artery, small artery and cardioembolic strokes).

Similarly, 17 highly expressed miRNAs, hsa-let-7e, miR-1184, -1246, -1261, -1275, -1285, -1290, -181a, -25*, -513a-5p, -550, -602, -665, -891a, -933, -939 and -923, have also been identified as highly expressed in the subtypes. miRNA profiling has been shown to potentially be an additional tool for the diagnosis outcome of stroke. miR-25*, miR-34b, miR-483-5p and miR-498 have been found to be downregulated in low-risk stroke patients (32). However, only miR-25* expression is detected, and it remains upregulated, in existing stroke-risk patients. These miRNAs are considered to be specific for the pathogenesis of stroke in low-risk stroke patients, suggesting a different molecular mechanism compared to stroke with pre-existing risk factors (32). Siegel *et al* (33) identified a different expression of miR-23a in males and females. miR-23a expression is evidently decreased following ischemia in males. Inversely, its expression is significantly increased following a stroke in females, thereby emphasizing the gender-specific miRNA expression in stroke patients (33).

The ionotropic glutamate receptors have been proven to be overstimulated by the accumulation of extracellular glutamate, which may mediate neuronal injury in stroke. miR-223 is expressed at a low level in the nervous system. Overexpression of miR-223 may decrease the expression of the glutamate receptor subunits, GluR2 and NR2B, and protect the brain from neuronal cell death (34). By contrast, miR-223 deficiency induces higher levels of GluR2 and NR2B, which

Table II. Targets and function of abnormal miRNAs in neurological diseases.

Disease	miRNA	Regulation	Target	Function	Refs.
Cerebral ischemia	miR-497	Upregulated	Bcl-2/-w	Inhibit apoptosis	(21)
	miR-132	Downregulated	MeCP$_2$	Enhance tolerance	(19)
	miR-200	Upregulated	PHD2/HIF-1	Improve cell survival	(18)
	miR-29c	Downregulated	DNMT3a	Inhibit cell death	(22)
	miR-199a	Downregulated	Sirt1	Enhance tolerance	(24)
	miR-146	Upregulated	TRAF-6, IRAK-1	Inflammatory responses	(17)
	miR-15b	Upregulated	Bcl-2	Inhibit apoptosis	(26)
	miR-203	Upregulated	phospho-Akt	Promote cell survival	(27)
Stroke	miR-223	Downregulated	GluR2/NR2B	Increase cell death and excitotoxicity	(32)
	miR-145	Upregulated	superoxide dismutase-2/ IFN-b	Mitigate oxidative stress and inflammation	(20,33)
	Let7f	Upregulated	IGF-1	Increase infarct volume	(34)
	miR-21	Upregulated	Faslg	Suppress apoptosis	(35)
	miR-181	Upregulated	GRP78	Aggravate injury	(36)
	miR-124a	Downregulated	JAG-Notch pathway	Inhibit proliferation and promote differentiation	(37)
AD	miR-29a/b-1	Downregulated	BACE1		(41)
	miR-107	Downregulated	BACE1		(44)
	miR-146a	Upregulated	CFH	Reduce inflammation	(46)
	miR-30a-5p	Downregulated	BDNF		(47)
PD	miR-133b	Downregulated	Pitx3	Enhance dopamine release	(51)
HD	miR-9/9*	Downregulated	REST/CoREST		(54)
	miR-22	Downregulated	Rcor1/Rgs2/HDAC4, Tp53inp1/MAPK14/p38	Decrease HD-related effects and apoptosis	(58)
Epilepsy	miR-134	Upregulated	Limk1	Reduce spine volume and shorten dendritic length	(60)
	miR-221/-222	Downregulated	ICAM1	Immune response	(63)
	miR-34a	Upregulated	Caspase-3	Increase survival and reduce apoptosis	(62)
Traumatic injury	miR-486	Upregulated	NeuroD6	Decrease apoptosis	(69)

miRNA, microRNA; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease.

lead to an increase in neuronal cell death. These data suggest that miR-223 exerts a neuroprotective effect by regulating the expression and function of GluR2 and NR2B in stroke patients. A high expression of miR-145 is induced by stroke and superoxide dismutase-2 is one of the downstream targets (21). The knockdown of miR-145 increases the expression of super-oxide dismutase-2, which may attenuate neuroprotection. Interferon-β, an anti-inflammatory cytokine that may decrease infarction, is also a target of miR-145 (35). Therefore, miR-145 mitigates oxidative stress and inflammation that contribute to post-ischemic brain death. Let7f and miR1 can inhibit neuro-protection by regulating insulin-like growth factor 1, which is an endogenous neuroprotectant (36). Notably, anti-miR1 treatment is known to significantly decrease the infarct volume in the cortex, whereas anti-Let7f reduces the infarct volume in the cortex and striatum. Anti-Let7f treatment has been suggested to be more effective in inducing neuroprotec-tion following stroke compared to anti-miR1. Therefore, the

Let7 family is likely to be a stronger therapeutic target for stroke. Buller *et al* (37) reported that stroke increases miR-21 expression by ~3-fold in the ischemic boundary zone *in vivo*. When overexpressed *in vitro*, miR-21 suppresses oxygen and glucose deprivation-induced apoptosis. The main reason for this is that miR-21 downregulates the expression of the target, FAS ligand, an important cell-death ligand, and mediates the neuroprotective effect.

In the murine stroke model, the expression of miR-181 increases where the cells die, the core, but decreases where the cells survive, the penumbra (38). The multiple roles of glucose-regulated protein (GRP)-78, a member of the heat-shock protein 70 family, in cellular protection is vali-dated as a target of miR-181 by the dual luciferase assay. An increased expression of miR-181a is associated with a decrease of the GRP78 protein level and aggravates injury *in vitro* and *in vivo*. By contrast, the reduction of miR-181a is associated with reduced injury and increased GRP78 protein levels. These

results demonstrate that miR-181 levels change in response to stroke, and reducing miR-181 protects the brain from stroke by manipulating GRP78. miR-124a is reduced in the subventricular zone neural progenitor cells *in vivo* (39). *In vitro*, miR-124a inhibits progenitor cell proliferation and promotes neuronal differentiation by targeting the jagged-Notch signaling pathway. These data provide novel insights into the molecular mechanisms underlying stroke-induced neurogenesis.

miR-210 plays critical roles in stroke. The study by Zeng *et al* (40) evaluated the correlation of blood miR-210 with clinical findings in acute ischemic stroke. miR-210 was evidently decreased in the blood of the stroke patients, particularly at 7 and 14 days of stroke onset. The miR-210 level in stroke patients with a positive outcome was higher than patients with a poor outcome. Therefore, blood miR-210 is a sensitive biomarker for the clinical diagnosis and prognosis in acute cerebral ischemia. miR-210, a pleiotropic hypoxia-microRNA, is positively correlated with an improved prognosis, becoming a sensitive biomarker for clinical diagnosis and prognosis in acute ischemic stroke. Additionally, miR-125b and anti-inflammatory (miR-26a, miR-34a, miR-145 and let-7b) miRNA are reported to positively influence stroke outcomes (41). The aforementioned results indicated that the miRNA profiles are specific to stroke pathogenesis and that miRNA expression patterns may be useful in the identification of stroke subtypes and functional outcomes.

4. Neurodegenerative diseases

Neurodegenerative diseases result in the gradual and progressive loss of neuronal tissues and cells, leading to significant motor and cognitive disability. The most distinct characteristics are the formation of pathological changes in the brain, including extracellular protein deposits, cellular inclusions and change of cell morphology. Thus far, with few exceptions, there are no effective tools in existence that can clearly diagnose the presence, absence or category of a neurodegenerative disease. The aberrant expression of miRNAs has been found in neurodegenerative diseases, showing that miRNAs are involved in these diseases, including AD, PD and HD (42) (Table I).

5. Alzheimer's disease

Previous studies have reportedly found a number of altered miRNAs in human AD tissue and models of AD. In total, 328 miRNAs have been profiled in the anterior temporal cortex of five AD patients, showing a decrease of 13 miRNAs (43). Cogswell *et al* (44) previously evaluated the regional and stage-specific deregulation of miRNA expression in AD. Approximately 300 miRNAs were detected in the hippocampus, medial frontal gyrus and cerebellum from early- and late-stage AD compared to the control. Of these, miR-423 expression was upregulated in the hippocampus, whereas miR-98 was downregulated in the cerebellum.

miR-298 and miR-328 play important roles by repressing the expression of β-amyloid precursor protein-converting enzyme 1 (BACE1), which causes amyloid-β (Aβ) overproduction in cultured neuronal cells (43). The miR-29a/b-1 cluster is decreased in sporadic AD patients, and it has been demonstrated that miR-29a/b-1 also regulates BACE1 expres-

sion (43). The study by Wang *et al* (46) demonstrated that miR-107 expression is decreased significantly in the cortex of AD patients, even at extremely early pathological alterations. Furthermore, the decrease of miR-107 is correlated with an increase of BACE1 expression. By contrast, miR106a and miR-520c negatively regulate the expression of APP 3'-UTR by dual-fluorescence reporter genes (47). In addition, overexpression of miR-106a or miR-520c reduces APP levels by 50%. Therefore, it is suggested that the dysregulation of specific miRNAs may be a cause of AD by the modulation of APP and BACE1 expression.

miR-146a is upregulated in human AD brain tissue, and an interaction between miR-146a and complement factor H has been validated, suggesting the possibility that the inhibition of miR-146a leads to a reduction in disease-related inflammation (48). Using the neuropeptide Y (NPY) pre-treated rat cortical neurons of the AD model, miR-30a-5p expression was decreased and brain-derived neurotrophic factor (BDNF) expression was increased at 24 and 48 h, following exposure to Aβ (49). Therefore, Croce *et al* (49) suggested that miR-30a-5p regulates BDNF with a mechanism that possibly facilitates the neuroprotective effect of NPY in rat cortical neurons exposed to Aβ. These results revealed that dysregulated miRNAs are associated with the molecular pathways in AD pathogenesis, including neurogenesis, insulin resistance, oxidative stress and innate immunity.

6. Parkinson's disease

PD is associated with progressive neurodegeneration of dopaminergic neurons (DNs) in the substantia nigra and leads to tremor, rigidity and bradykinesia. miRNA profiling was performed in PD patients and normal controls. Among the 224 miRNAs identified, miR-133b, -218-2, -15b, -101-1, -107, -335 and -345 were downregulated significantly in PD patients (50). miR-34b/c expression was decreased in several affected brain regions of PD (51). miR-7 and miR-153 have been proven to negatively regulate the level of α-synuclein, which is accumulated post-transcription in PD patients (52). Martins *et al* (53) found that 18 miRNAs were differentially expressed in peripheral blood mononuclear cells. A total of 662 genes were predicted to target 11 miRNAs and were revealed to represent pathways that have been previously linked to PD, as well as novel pathways (53).

miR-133b is deficient in PD midbrain DNs, as well as in murine PD models. In *in vitro* experiments, the knockdown of miR-133b enhanced the expression of DN markers and depolarization-induced dopamine release. However, overexpressed miR-133b inhibited the differentiation of DNs, causing a decrease in dopamine release (54). Pitx3, a transcription factor, is necessary for midbrain dopaminergic maturation and function. Kim *et al* (54) further demonstrated that miR-133b regulates Pitx3 by a negative-feedback circuit; Ptx-3 transcribes miR-133b, which in turn represses Ptx-3 translation. In another study, the miR-433 targeting sites in fibroblast growth factor 20 were disrupted by the presence of the T allele, resulting in an increase of α-synuclein expression (55), which may cause PD by overexpression and point mutations.

Blood samples have been demonstrated to be a useful source for PD-associated miRNA identification, and six

differentially-expressed miRNAs have been revealed. Of these, the expression levels of miR-1, miR-22* and miR-29 may distinguish between non-treated PD and healthy subjects, while miR-16-2*, miR-26a-2* and miR30a differentiate treated from untreated patients (56). A novel mechanism of PD risk in which the variations of gene translation associated with PD interfere with the regulation of miRNAs is suggested.

7. Huntington's disease

HD is a fatal hereditary neurodegenerative disease caused by a CAG-repeat expansion in the Huntingtin gene, which produces a toxic polyglutamine in the Huntingtin protein. The profiles and regulation of miRNAs in HD are relatively less to other neurodegenerative diseases, and have not been studied completely. The miRNAs that are altered in HD disease include miR-9/9*, miR-124a and miR-132, which are repressed in the brains of human HD patients and murine models. Notably, miR-9/9* exerts a biofunction by regulating the REST complex, and in particular, miR-9 targets REST while miR-9* targets CoREST (57). Of note is the double-negative feedback loop between the REST-silencing complex and the miRNAs that are being regulated.

Lee *et al* (58) detected the miRNA expression and regulators in the YAC128 and R6/2 murine transgenic models of HD. In the YAC128 murine model, upregulated miRNAs were evident at 5 months, and downregulated miRNAs were exhibited at 12 months. Therefore, the miRNA regulators, Drosha-DGCR8, Exportin-5, and Dcp1, were increased at 5 months, while Dicer was reduced at 12 months. In the R6/2 murine model, the decrease of miRNA was accompanied by an increase of Drosha at 10 weeks. Nine miRNAs were downregulated in the 12-month-old YAC128 and 10-week-old R6/2 mice, including miR-22, miR-29c, miR-128, miR-132, miR-138, miR-218, miR-222, miR-344, and miR-674*. miR-22 was also significantly downregulated in HD. Previously, it was proven that miR-22 targets multiple mRNAs involved in HD pathogenesis, including Rcor1, Rgs2 and HDAC4. Rcor1 is involved in the restrictive element 1 silencing transcription factor pathway, leading to a large-scale repression of neuronal genes in affected neurons (59). Rgs2 expression is protective in the *in vitro* models of HD by decreasing ERK activation (60). HDAC4 has been shown to improve the neurodegeneration in cellular and animal models of HD (61).

miR-22 also inhibits neuronal apoptosis, at least in part, by decreasing the expression of pro-apoptotic proteins, including Tp53inp1 and MAPK14/p38. The aforementioned results show that miR-22 has therapeutic potential due to specific HD-related effects or/and anti-apoptotic pathway (62). This suggests that abnormal miRNA may aid in the therapeutic application for HD in future studies.

8. Epilepsy

Epilepsy is a common brain disorder that is characterized by seizures. Epileptic seizures generate abnormal, excessive or hypersynchronous neuronal activity in the brain. Although epilepsy is usually controlled with medication, it is currently difficult to cure.

miR-134 is a brain-specific and activity-regulated miRNA. In hippocampal neurons, miR-134 targets LIM domain kinase 1 (Limk1), which regulates dendritic spine dynamics, thereby inhibiting Limk1 translation. Overexpression of miR-134 reduces spine volume *in vitro,* and shortens the total dendritic length (63) and abrogates long-term potentiation *in vivo* (64). In a rat model of temporal lobe epilepsy, 24 miRNAs have been found to be deregulated in the hippocampus, including 10 upregulated miRNAs (miR-23a, -27a, -31, -33, -34a, 146a, -152, -203, -210 and -211) and 14 downregulated miRNAs (miR-19a, -135b, -136, -138*, -144, -153, -190, -296*, -301a, -325-5p, -380, -542-3p, -542-5p and -543) (65). Bioinformatics analysis revealed that the majority of deregulated miRNA targets are the important components of the KEGG pathway, which is known to participate in the regulation of epilepsy. Of these miRNAs, miR-34a was detected to significantly increase at 1 day, 7 days and 2 weeks post-status epilepticus and at 2 months following temporal lobe epilepsy. The miR-34a antagomir has been proven to exert an inhibitory effect on the caspase-3 protein, which may contribute to increased neuronal survival and reduced neuronal death or apoptosis.

In total, 165 miRNAs were detected to be aberrantly expressed in mesial temporal lobe epilepsy (MTLE). Furthermore, deregulated miRNAs are prominently targeted by immune proteins. For example, miR-221 and miR-222 are found to regulate intercellular adhesion molecule 1 (ICAM1) expression and are co-expressed with ICAM1 in astrocytes in MTLE patients (66). Aberrant miRNA in MTLE has been suggested to affect the expression of immunomodulatory proteins, by facilitating the immune response. The study by Peng *et al* (67) assessed the expression patterns of brain-specific miR-124 and miR-134, and inflammation-related miR-21 and miR-132 at the three stages of MTLE. miR-124 and miR-134 showed similar expression patterns of dynamics at the three stages of MTLE development. However, miR-21 and miR-132 were significantly upregulated in the acute and chronic stages, whereas in the latent stage, miR-21 was downregulated and miR-132 was upregulated. The upregulation of miR-124 and miR-134 suggests that they are potential targets for anticonvulsant drugs in the epileptic developing brains. However, the differential expression of miR-132 and miR-21 suggests different functions by modulating various targets in MTLE pathogenesis. In focal-onset status epilepticus, the expression of 21 miRNAs was increased, and the expression of 12 miRNAs was reduced (68). Of these, miR-132 was differentially upregulated. The depletion of miR-132 reduces seizure-induced neuronal death, suggesting that miRNAs are important modulators of this mechanism. Thus, the regulation mechanism of miRNA may enrich the current epilepsy pathogenesis at the level of miRNA-mediated regulation.

9. Traumatic injury

Traumatic brain injury (TBI) is recognized as a leading worldwide cause for mortality and permanent neurological disability. The pathophysiology of TBI is complex and a number of different signaling pathways are involved in the damage of the brain.

miRNA expression studies have shown that miRNAs play a vital role in the traumatic brain injury process post-injury.

In rat and mouse hippocampi, 50 miRNAs have been shown to decrease and 35 miRNAs increase following controlled cortical impact injury (69). Bioinformatics analysis revealed that the predicted targets of these miRNAs are involved in the biological processes and functions that are initiated following injury, including transcriptional regulation, signal transduction, proliferation and differentiation (Tables I and II).

The expression of miR-21 was significantly upregulated in the hippocampus following TBI (70). The potential targets of miR-21 are involved in enzyme-linked receptor signaling, transcriptional regulation and developmental processes. This suggests that miR-21 expression in the hippocampus may affect multiple components of TBI pathophysiology. miR20a may cause continuing motor neuron degeneration when overexpressed in spinal cord injury (SCI) (71). Blocking miR20a in SCI animals effectively induces definitive motor neuron survival and neurogenesis, and improves the functional deficit. These results suggest that miR20a is a potential target for therapeutic intervention following SCI. Traumatic injury induces miR-486 upregulation in a murine model of spinal cord injury (72). Additionally, miR-486 is significantly increased by the accumulation of reactive oxygen species (ROS) *in vitro* and *in vivo*. Subsequently, ROS as a final product of miR-486 participates in a positive-feedback circle for miR-486 overproduction. Neurogenic differentiation 6 (NeuroD6), an important target of miR-486, plays a neuroprotective role in ROS-mediated apoptotic neuronal cell death. The inhibition of miR-486 upregulates NeuroD6 expression, which decreases apoptosis and reduces the functional deficits. Knocking down miR-486 or infusing NeuroD6 recovers the hind limb reflexes more rapidly, and a higher percentage of these mice regain motor function. Therefore, miR-486 is a potential therapeutic target through the neuroprotection of NeuroD6 for spinal cord injuries.

The study by Hu *et al* (73) assessed the miRNA expression and their corresponding regulation pathway in the pathophysiology of traumatic brain injury. Eight miRNAs were upregulated and 13 miRNAs were downregulated at 24 h after the controlled cortical impact injury. The targets of upregulated miRNAs are involved in cell proliferation and differentiation, chromatin remodeling, protein synthesis and processing, and synaptic transmission. Downregulated miRNAs target aerobic respiration, alternative splicing, protein maturation, androgen signaling and intracellular signaling pathways. Multiple miRNA have been suggested to cooperatively regulate signaling pathways for the pathological changes of brain injury. The distinctive miRNA expression profiles may be used as molecular signatures to appraise TBI progression.

10. Conclusion

The occurrence and development of central nervous system (CNS) diseases are accompanied by the altered expression of miRNAs. The role of altered miRNA is elucidated based on their expression in CNS and the prediction of their targets with the latter being validated *in vitro* and *in vivo*. The evaluation of miRNA expression produces novel molecular information, and introduces the possibility that expressing or inhibiting specific miRNAs may improve the disease process. Considering that a miRNA molecular may inhibit the expression of a number

of target genes, elaborating the molecular mechanisms of the miRNA network within the same cellular pathway is likely to be critical in a number of CNS diseases. This may provide a possibility to modulate the miRNA activity and function for disease modification of numerous incorrigible disorders. In particular, treatment for multigenic diseases requires the modulation of multiple targets or pathways. Advances in the miRNA field in recent years have led to identification of potentially novel prospects in solving the fundamental causative factors in incurable CNS diseases.

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