MicroRNAs: protective regulators for neuron growth and development

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Abstract

MicroRNAs (miRNAs) play an important regulatory role in neuronal growth and development. Different miRNAs target different genes to protect neurons in different ways, such as by avoiding apoptosis, preventing degeneration mediated by conditional mediators, preventing neuronal loss, weakening certain neurotoxic mechanisms, avoiding damage to neurons, and reducing inflammatory damage to them. The high expression of miRNAs in the brain has significantly facilitated their development as protective targets for therapy, including neuroprotection and neuronal recovery. miRNA is indispensable to the growth and development of neurons, and in turn, is beneficial for the development of the brain and checking the progression of various diseases of the nervous system. It can thus be used as an important therapeutic target for models of various diseases. This review provides an introduction to the protective effects of miRNA on neurons in case of different diseases or damage models, and then provides reference values and reflections on the relevant treatments for the benefit of future research in the area.

Key Words: brain damage; miRNA; neurodegenerative disorders; neuronal apoptosis; neuronal protection

Introduction

MicroRNAs (miRNAs) are endogenous, 18–22 nucleotide, non-coding ribonucleic acid (RNA) molecules that function as post-transcriptional regulators of gene expression. By binding to miRNAs, specifically at the 3′-untranslated region (3′-UTR) through perfect or imperfect complementation, miRNAs induce either translational repression or RNA degradation in cells (Ambros, 2004; Rana, 2007). The dysregulation of miRNA expression has been observed in many neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, neurological disorders, and epilepsy. Neurodegeneration and death are important markers of neurodegenerative diseases. The importance of miRNA in the nervous system has been reported in many studies in recent years, and an increasing amount of evidence of miRNA dysregulation in the case of neurological diseases is becoming available. Understanding the expression and activity of these miRNAs may contribute to the development of new therapies (Karnati et al., 2015). During the development of the nervous system, a large number of neurons must undergo apoptosis over a period for them to precisely match their respective target cells (Oppenheim, 1991). However, once the corresponding neuron has connected to its specific target cell, its apoptotic program must be strictly controlled because these neurons cannot regenerate, and have limited survival and function in the body (Benn and Woolf, 2004). miRNAs are small, non-coding RNAs that regulate gene expression (Bartel, 2009). Here, we examine whether miRNAs can play a protective role as a key regulator in the growth and development of neurons, and whether they can be a target for therapeutic intervention (Figure 1).

Database Search Strategy

The authors used a number of criteria to include research in this review. Studies discussing the effects of miRNAs as protective regulators of neuronal growth and development were considered. The full text of English-language articles published from January 2015 to June 2022 were included in this non-systematic review. The models of diseases considered pertained to the type of injury associated with miRNA. The authors searched the PubMed database to identify the relevant publications. The strategies for literature retrieval were as follows: The terms (1) “miRNA” and (2) “neuron” were combined with (a) “neuron protection” and (b) “neurodegenerative diseases,” such as in “miRNA protective effect on neurons i.e., (1) + (a), and protective effect of miRNA on neurons in the mechanism of neurodegeneration,” i.e., (1) + (b). We used four queries. We screened the list of references included in each study to identify other studies that might be useful. We first screened the titles and abstracts of papers, and then search their full text for keywords, such as “neuron protection” and “nerve injury,” to find ones that might be appropriate. The process of data extraction focused on information on each type of injury examined and the protective role played by miRNA.

Role of MicroRNAs in Brain Development

The discovery of miRNA-mediated gene regulation has led to a deeper understanding of the regulatory mechanisms of gene expression in the last decade. Several studies have investigated the role and regulation of miRNA in brain development. The potential of miRNAs to regulate individual gene expression provides brain cells, especially neurons, with the ability to control gene expression from their upstream and downstream sites. This is a prerequisite for the formation of the developing brain (Kiecker and Lumsden, 2005). miRNAs play significant roles in brain development, IPSCs, stemness, epithelial-to-mesenchymal transformation, and the maturation of different types of cells (Kapranov et al., 2010). Each step of brain development is tightly regulated and requires a specific network of gene regulatory mechanisms. The brain expresses the highest number of unique miRNAs of all organs of the body, which suggests that they have some physiological and metabolic significance (Mott et al., 2012). miRNAs are an important regulatory factor in the basic processes of brain development, such as neuronal apoptosis, neuronal differentiation, and neuronal proliferation (Singh et al., 2014; Jauhari et al., 2017). They also constitute an important regulatory factor in peripheral nerve regeneration (Mahar and Cavalli, 2018). A large number of miRNA analyses and Dicer knockout studies have demonstrated that miRNA expression plays an extremely important role in brain development (Ambros, 2004; Bak et al., 2008; Petri et al., 2014, Figure 2).

Role of MicroRNAs in Diseases

Cerebral ischemia/reperfusion injury

Cerebral ischemia/reperfusion injury (CIRI), which is caused by cardiac arrest, shock, stroke, cardiopulmonary bypass during anesthesia, and surgery, is the leading cause of disability and mortality worldwide (Donnan et al., 2008; Pang et al., 2022). The pathophysiological mechanisms of cerebral ischemia/reperfusion injury-induced neuronal damage are complex cellular events involving apoptosis- and oxidative stress-related pathways (Moskowitz et al., 2010). Many studies have elucidated the role and mechanism of miRNAs in cerebral ischemia and related diseases, which makes them a potential target for the diagnosis and treatment of CIRI (Rink and Khanna, 2011; Zhu et al., 2016, Table 1).
The effects of miRNAs secreted by different cell sources on neurons. miRNAs are derived from different types of cells, including macrophages, stem cells, exosomes, astrocytes, oligodendrocytes, microglia, cardiomyocytes, skeletal muscle cells, nerve cells, vascular smooth muscle cells, and various mediators in vivo. The different types of cells reported in this paper can secrete different subtypes of miRNA, and changes in miRNA expression can affect downstream target genes or signaling pathways, thus affecting the development and survival of neurons. Neurons can be damaged by apoptosis, necrosis, neuronal loss or axon rupture, inflammatory injury, toxic medium injury, or death due to the influence of the nutritional environment. miRNA, as a therapeutic target of neuronal injury, can ameliorate the above-mentioned injuries and improve the course of the disease. miRNA: MicroRNA.

Figure 1 | The effects of miRNAs secreted by different cell sources on neurons.

miRNAs can be used as a therapeutic target to reverse neuronal injury. miRNA: MicroRNA.

However, it has been reported that the inhibition of miR-181 expression in mouse models can reduce the size of the infarct, improve the neuronal function deficit, and reduce neuronal loss induced by forebrain ischemia (Xu et al., 2015). The injection of the miR-181-3p antagonist into the brain of a rat upregulates the expression of Bcl-2 and GLT-1, thereby inhibiting neuronal cell death in case of forebrain ischemia (Moon et al., 2013). The overexpression of miR-592 in neurons reduces the level of p75NTR, which indicates that the down-regulation of endogenous miR-592 in neurons can inhibit neuronal cell death in case of forebrain ischemia (Zhu et al., 2014). The upregulation of miR-25 inhibits cerebral ischemic injury (Zhu et al., 2014). miRNA expression can be changed by different types of factors, including inhibitors, activators, pharmaceutical agents, and physical or chemical stimuli in vitro. The amount secreted in the body includes that in exosomes, stem cells, tissue cells, glial cells, and receptor mediators. These factors change the expression of miRNA, which targets its downstream genes or signaling pathways, and ultimately leads to changes in the neurons. This in turn affects the development and survival of neurons. Furthermore, we found that miRNA can be used as a therapeutic target to reverse neuronal injury. miRNA: MicroRNA.

Figure 2 | Changes in miRNA expression affect neuronal development and survival.

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oxidative stress by upregulating manganese superoxide dismutase (MnSOD) and extracellular superoxide dismutase (Liu et al., 2015). Our observations are in agreement with those of Zhao et al. (2014), whereby miR-23a-3p reduces neuronal cell death and apoptosis as indicated by decreased lactate dehydrogenase leakage and caspase-3 activity in miR-23a-3p overexpression of miR-23a-3p in neuro-2a cells upon H2O2-induced oxidative stress. This study indicated that miR-23a-3p suppresses oxidative stress and reduces CII. Ginsenoside Rg1 inhibits the expression of miR-144 and promotes the caspase-3 cleavage of the ARE pathway, thereby reducing oxidative stress and protecting neurons after I/R (Chu et al., 2019). Stary et al. (2015) reported that the inhibition of miR-200c and upregulation of Reelin expression may ameliorate acute brain injury and enhance recovery.

Apolipoprotein lipoprotein particles shuttle miRNAs from astrocytes to neurons, leading to the inhibition of cholesterol biosynthesis cholesterol in high acetylation. They also inhibit the expression of HMGCR to block cholesterol synthesis in neurons. The accumulation of the substrate-adduct HMG-CoA increases histone acetylation in neuronal nuclei, upregulates interferon γ early genes and improves. Interferon γ and chemical stimuli increase endogenous miRNA expression and down-regulating DDR1 in case of cerebral ischemia injury. The reduced miR-129 (Mao et al., 2018) is found to increase miR-381 expression and reduce IRF4 expression in MCAO rats. Moreover, DEX has been found to increase miR-381 expression and reduce IRF4 expression in MCAO rats to reduce interleukin-6 (IL-6) expression in turn, which suppresses the inflammatory response and cell apoptosis both in vivo and in vitro (Chu et al., 2019). Our observations are in agreement with those of Li et al. (2021a) that the overexpression of miR-27a-3p significantly reduces cerebral I/R damage by targeting FOXO1, which provides a new direction for future research on cerebral I/R therapy. A study on the role of miR-193b-3p expression in rats revealed that miR-193b-3p has neuroprotective effects against focal CII in cultured neurons. These neuroprotective effects are likely mediated by the inhibition of 5-LOX. These findings indicate that miR-193b-3p can be used as an agent for the treatment of focal CII (Chen et al., 2020). It has been reported that melatonin plays an anti-inflammatory and CII-improving protective role by regulating the miR-26a-5p-NRF2 axis and the JAK2-STAT3 pathway, which may provide new ideas for the treatment of CII-related ischemic stroke and other diseases of the central nervous system (Yang et al., 2020a). In lower motor neurons, vascular smooth muscle cells, and various mediators important for the remodelling of endogenous miRNA expression can be changed by different types of factors, including inhibitors, activators, pharmaceutical agents, and physical or chemical stimuli in vitro. The amount secreted in the body includes that in exosomes, stem cells, tissue cells, glial cells, and receptor mediators. These factors change the expression of miRNA, which targets its downstream genes or signaling pathways, and ultimately leads to changes in the neurons. This in turn affects the development and survival of neurons. Furthermore, we found that miRNA can be used as a therapeutic target to reverse neuronal injury. miRNA: MicroRNA.
150, which directly promotes the concept of protecting the function of the central nervous system by activating the ERK1/2 axis to influence the survival and function of cerebral cortical neurons. In the early stage of focal cerebral ischemia, the level of miR-124-mediated pro-survival p53 signaling protein IASPP decreases. This pathway should be investigated as a new therapeutic approach for promoting neuronal survival in the case of stroke and brain injury (Liu et al., 2013). M2 microglia-derived exosomes have been reported to attenuate ischemic brain injury and promote neuronal survival via exosomal miR-124 and its downstream target USP14. M2 microglia-derived exosomes represent a promising avenue for treating ischemic stroke (Zhong et al., 2018), where this has significant potential for clinical applications (Yang et al., 2017).

This study suggests that the glycoprotein-exosomes of the rabies virus can be therapeutically utilized for the targeted delivery of gene drugs to the brain, thereby promoting neuronal survival and regeneration after ischemic stroke. Therefore, miR-132 reduces ischemia-induced neuronal death and may serve as a novel therapeutic target to ameliorate neuronal death and may serve as a novel therapeutic target to ameliorate neuronal injury by robust cortical neurogenesis. A study by Chang et al. provides evidence that miR-195 can downregulate KLF5 and its downstream target USP14. M2 microglia-derived exosomes represent a promising avenue for treating ischemic stroke (Zhong et al., 2018), where this has significant potential for clinical applications (Yang et al., 2017).

We have seen similar reports to the above in the last 2 years. Cell-derived exosomes from exercise mice can protect neurons from hypoxia-induced apoptosis and axon growth. Overexpression of miR-126 and P3K in vitro can also achieve the same function (Wang et al., 2020b). The study by Yasmeen et al. (2019) provides evidence that HCMVEC/D3 cells transfected with miR-27a-3p and miR-222-3p mimics can reduce the relative expression of PDE3A protein, and regulating its expression may improve the progression of cerebral ischemia disease. In-vitro validation experiments have shown that blocking the maternally expressed gene 3 that specifically binds to miR-378 can downregulate the expression of GRB2, and in turn, promotes the activation of the Akt/mTOR pathway. These results suggest that miR-378 may have protective effects on neuronal autophagy and nerve function injury (Luo et al., 2020). The high expression of miR-126 in EPC-EX alleviates acute brain injury and promotes neurological recovery in the case of diabetic ischemic stroke, providing an active strategy to enhance the therapeutic effect of EPC-EX, and thus may lead to a new, cell-free treatment for diabetic stroke (Wang et al., 2020c). miR-137 has a neuroprotective effect on ischemic stroke by weakening oxidative, apoptosis, and inflammation pathways by inhibiting the SRC-dependent MAPK signaling pathway (Tian et al., 2021). The inhibition of miR-668 can inhibit neuronal apoptosis by regulating the mitochondrial function and the NLRP3 signaling pathway, namely, by improving the expressions of the caspase 3, Bax, and Bcl-2 proteins in I/R stroke rats (He et al., 2020). Exosomes miR-146b is an important neuroregulatory factor in neurogenesis as it promotes endogenous neural stem cell differentiation in neurons around post-stroke ischemia. Electroacupuncture promotes endogenous neural stem cell differentiation by stimulating the expression of the exosome miR-146b, thus improving nerve injury after ischemic stroke (Zhang et al., 2020d). It has been reported that circ-HECTD1 knockdown inhibits the expression of TRAF3 by targeting miR-133b, thereby attenuating neuronal injury caused by cerebral ischemia (Dai et al., 2021). The inhibition of miR-130a improves neural functional recovery in MCAO rats, alleviates nerve injury, increases cerebral angiogenesis, promotes neuronal activity, and inhibits apoptosis by regulating its target gene XIAP (X-linked inhibitor of apoptosis protein) in both animal models and cellular models (Deng et al., 2020). The inhibition of BCL6 can alleviate oxidative stress-induced neuronal injury and reduce the area of cerebral infarction in IS mice by targeting the miR-31/PKD1 axis. This can be achieved by down-regulating PKD1 and inhibiting the activation of the JAK2/STAT3 pathway, thus alleviating OGD-induced cell injury (Wei et al., 2021). The study by Chang et al. provides evidence that miR-195 can downregulate KLF5 and its downstream target USP14. M2 microglia-derived exosomes represent a promising avenue for treating ischemic stroke (Zhong et al., 2018), where this has significant potential for clinical applications (Yang et al., 2017).
| miRNA | Target | Target trend | Effect | Reference |
|-------|--------|--------------|--------|-----------|
| miR-29b↑ | Arachidonic acid | ↑ | Attenuate the loss of neurons | K汉na et al., 2013 |
| miR-150↓ | ERK1/2 | ↓ | Protect cerebral cortical neuron function and affect the survival and function of cerebral cortical neurons | Li et al., 2019 |
| miR-124↑ | iASPP | ↓ | Promote neuronal survival in stroke and brain injury | Liu et al., 2013 |
| miR-124↓ | USP14 | ↑ | Attenuate ischemic brain injury and promote neuronal survival | Song et al., 2018 |
| miR-19a-3p↓ | ADIPOR2 | ↑ | Mitigate IR-mediated repression of glycolysis enzymes expression, glucose uptake and lactate production, and neuronal apoptosis | Ge et al., 2019 |
| miR-9↑ | HDAC4 | ↑ | Conducive to neuronal survival and regeneration | Nampoothiri and Rajanikan, 2019 |
| miR-124↑ | REST-USP14 | ↓ | Regulate neuronal differentiation | Doepner et al., 2013 |
| miR-9↓ | Bcl2l11 | ↑ | Promote neuronal apoptosis | Chen et al., 2017 |
| miR-132↑ | CA1 | ↓ | Ameliorate the neurodegeneration and cognitive deficits associated with ischemic stroke | Hwang et al., 2014 |
| miR-124↑ | Lamp2b/RVG-exosomes | ↓ | Promote cortical neural progenitors to obtain the neuronal identity and protect against ischemic injury by robust cortical neurogenesis | Yang et al., 2017 |
| miR-126↑ | BDNF/Tkrib/P13K/Akt | ↑ | Moderate treadmill exercise prior to ischemic stroke-elicted beneficial effects, including reducing brain cell apoptosis in the acute stage and improving sensorimotor function by enhancing angiogenesis and neurogenesis in the chronic stage | Wang et al., 2020c |
| miR-27a-3p/miR-222-3p↑ | PDE3A | ↓ | Regulate the immune response, neurogenesis, and signaling pathways relevant for cell survival, repair processes, and endothelial integrity | Yasmeen et al., 2019 |
| miR-378↑ | MEG3/GRB2/Akt/mTDR | ↓ | Inhibit neuronal loss and neurological functional impairment in mice as well as neuronal autophagy and death | Lu et al., 2020 |
| miR-126↑ | EFC-Exs | ↑ | Attenuate acute injury and promote neurological function recovery | Wang et al., 2020b |
| miR-137↑ | Src/MAPK | ↓ | Inhibit the secretion of inflammatory factors, suppress oxidative stress, and reduce apoptosis of astrocytes | Tian et al., 2021 |
| miR-9↑ | Bcl2l11 | ↑ | Rescue the abnormalities in the MCAO mice model and the cell apoptosis both in vivo and in vitro | Wei et al., 2016 |
| miR-668↓ | NLRP3/20-I | ↑ | Prevent neuronal apoptosis | He et al., 2020 |
| miR-31↑ | NeuroD1 | ↓ | Inhibit neuronal differentiation into neurons in peri-ischemic striatum | Zhang et al., 2020d |
| miR-133b↑ | TRAF3/3/circ-HECTD1 | ↑ | Reduce cerebral infarction volume and inhibit neuronal apoptosis in MCAO mice | Duan et al., 2021 |
| miR-130a↓ | XIA | ↑ | Improve the neurological function, alleviate nerve damage, increase the number of new vessels in brain tissues of rats with MCAO, promote neuronal viability, and suppress apoptosis | Deng et al., 2020 |
| miR-31↑ | BCL6/PK2D | ↓ | Reduce the size of cerebral infarct and oxidative stress levels in i5 mice and reduce the rate of apoptosis and increase the rate of cell survival | Wei et al., 2021 |
| miR-195↑ | KLF5/SN | ↓ | Inhibit neuronal apoptosis | Chang et al., 2020 |

**Hypoxia-ischemic brain damage**

Hypoxia-ischemia is thought to be the final, common endpoint for a complex convergence of events. Some of these events are genetically determined and some are triggered by an in-utero (but not necessarily intrapartum) stressor (McClean and Ferrier, 2004; Table 3).

Sun et al. (2018a) reported that the upregulation of miR-592-5p and the suppression of the PGD2/DP signaling pathway can protect hippocampal neurons from hypoxic-ischemic brain damage (HIBD) in neonates. The administration of GW0742 after HI reduced the area of the infarct, attenuated neuronal apoptosis, and improved neurologic scores over a period of 1 week. The neuroprotective effects of GW0742 are related to the PPAR-β/δ/miR-23b and miR-27b clusters inhibited neuronal apoptosis induced by hypoxic-ischemic encephalopathy (HEI) (Gamdzyk et al., 2018). In a new mouse model of hypoxia-induced neuronal apoptosis, the overexpression of the miR-23b and miR-27b clusters inhibited neuronal apoptosis induced by intraperitoneal hypoxia. For the first time, the researchers discovered that miRNAs regulate the sensitivity of neurons to apoptosis during development and hypoxia-induced brain injuries (Chen et al., 2014).

A study by Zhou et al. (2020) revealed that IncRNA GASS absorbs miRNA-221 to promote neuronal apoptosis by upregulating PUMA/JNK/H2AX signaling under hypoxia. This finding deepens our understanding of the role of GASS in the pathogenesis of ischemic stroke, and may also provide a novel candidate for the treatment of stroke (Zhou et al., 2020). It is known that miR-146b-5p overexpression alleviates HEI-induced neuronal injury by inhibiting the IRAK1/TRA6/7AK1/NF-kB pathway. One study identified a new regulatory axis miR-146b-5p/IKE/7AK1/NF-kB in HEI, which is a promising therapeutic target for neuronal HEI (Yang and Zhao, 2020). The inhibition of miRNA-199a-3p expression in exosomes derived from hypoxia-induced glioma alleviates the peritumoral neurons in case of ischemic injury by inhibiting HIF-1α upregulation and promoting the expression of the mTOR pathway (Zhao et al., 2020). TCONS00004405 (Vi4) overexpression and miR-148-5p knockout promote neuronal survival and neurite growth, suppress cell apoptosis, and reduce motor and cognitive dysfunction in rats with HEI, while Igf-1bp3 intervention has the opposite effect. Vi4-miR-185-5p-Igfp-3p may be a drug target for HEI therapy (Xiong et al., 2020). The study by Xin et al. (2020) showed that miR-21a-5p is transferred to neurons and microglia in the damaged brain by the uptake of the mesenchymal stromal cells-derived extracellular vesicle (MSC-EV), which means that an important component of the neuroprotective properties of these MSC-EV is involved in targeting the mTOR gene. It has a neuroprotective effect in case of HI injury in newborn mice, which suggests that MSC-EV may provide a new treatment strategy for HEI (Xin et al., 2020). Slit2 is a target gene of miR-200b-3p. Hypoxia/ischemic brain damage in neonatal rats was alleviated by inhibiting miR-200b-3p via Slit2. Therefore, miR-200b-3p may be a potential therapeutic target for HIBD (Zhang et al., 2020c). HIBD in neonatal rats can result in acute and long-term cerebral dysfunction. The overexpression of miR-410-3p can promote neuronal survival and inhibit neuronal apoptosis to alleviate the motor, learning, and memory-related dysfunctions caused by HIBD. Thus, the overexpression of miR-410-3p may not only provide an effective treatment for neonatal HIBD, but may also provide novel insights into the clinical treatment or prevention of HIBD (Xiao et al., 2020). The upregulation of miR-21 can significantly reduce the volume of cerebral infarction in HIBD rats, reduce the degree of brain tissue injury, and improve neurobehavioral ability and memory by down-regulating CCL3, which has a protective effect on the brains of neonatal HIBD rats (Liu et al., 2020a).

**OGD/R-induced neuronal injury**

It is important to study the mechanism of ischemic neuronal injury to explore new therapeutic targets. The model of neuronal injury induced by OGD/R is a classic model for studying brain injury (Table 4). In the relevant procedure, pretreatment with sevoflurane alleviates miR-181a-induced cellular injury in primary cortical neurons after OGD/R by down-regulating miR-181a and upregulating XIAP. This has been identified as a direct target of miR-181a (Zhang et al., 2019b). The study by Duan et al. (2019) suggests that miR-135b-5p protects neurons against OGD/R-induced injury by down-regulating GSK-3β and promoting the Nrf2/ARE signaling pathway-mediated antioxidant responses. The inhibition of miR-153 protects neurons against OGD/R-induced injury by regulating NFκB/HIF-1α signaling, and suggests a potential therapeutic target for CIRI (Li et al., 2017). Previous studies have reported that miR-181a overexpression promotes lactate dehydrogenase release and apoptosis by reducing cell viability, and promotes damage to...
primary cortical neurons after OGD (Ouyang et al., 2012). Our observations are in agreement with those made by Zhang et al. (2019b), whereby FGDS-5A1 might protect neurons against OGD/R injury by acting as a ceRNA for miR-223 to mediate IGF1R expression. This implies the simultaneous down-regulation of miR-223 and overexpression of FGDS-AS1. IGF1R also exhibits the additional effects of extending OGD/R damage, increasing neuronal proliferation, and reducing neuronal apoptosis. Wang et al. (2017b) have suggested that miR-142-5p contributes to OGD/R-induced cell injury, and the down-regulation of miR-142-5p attenuates OGD/R-induced neuronal injury by promoting the M2 polarization of microglia. During ischemia, miR-1290 expression decreases while cav-1 expression may be upregulated in neurons, thereby increasing EV intake to protect them (Yue et al., 2019).

It has been reported that miR-133b down-regulates the expressions of IL-1α, IL-6, the tumor necrosis factor α, ELAVL1, NL-RP3, caspase-1, and IL-1β proteins to slow down the pyroptosis of neurons in newborn rats in a neuron model of OGD/R (Liu et al., 2020b). The study by Gao et al. (2020) illustrated that miR-29a-3p can enhance the viability of neuronal cells, obstruct lactate dehydrogenase activity, and reduce apoptosis after OGD/R treatment by negatively regulating the expression of TNFRSF1A through the inhibition of the nuclear factor-kB (NF-kB) signaling pathway. These findings provide insights into alleviating OGD/R-induced injury (Gao et al., 2020). It is known that IncRNA SNHG14 induces hypermitotic stress via the miR-182-5p/BNP3 axis in the hippocampal neurons of HT22 mice, thereby promoting OGD/R-induced neuronal injury. This may be a valuable target for cerebral I/R injury treatment (Deng et al., 2020). Neuronal cell growth is inhibited and neuronal cell apoptosis is promoted in the OGD/R model by reducing BDNF and attenuating the PI3K/Akt pathway. These findings contribute to uncovering the novel pathogenesis of ischemic brain injury (Hu et al., 2020). As a ceRNA, KCNQ1OT1 can reduce OGD/R-induced neuronal injury by preventing miR-153-3p from competing with Fox3. These findings provide insights into the molecular mechanism of CTRI. Targeting KCNQ1OT1 to regulate Fox3 may be a useful strategy to treat brain I/R injury (Wang et al., 2020a).

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH), which accounts for 10–15% of all cases of stroke, is the most devastating type of stroke that is highly associated with morbidity and mortality (Qureshi et al., 2001; Table 5). Post-ICH edema formation can lead to intracranial hypertension and herniation, and contributes to ICH-induced neurologic deficits and even fatality (Xi et al., 2002; Gong et al., 2004). The restoration of miR-27a-3p reduces brain edema, maintains the permeability of the blood-brain barrier, inhibits neuronal loss, and alleviates neurological deficits in rats with ICH. The protective effect of miR-27a-3p may be mediated by the inhibition of AQP11 in the endothelium of the capillaries of the brain (Xi et al., 2018). The overexpression of miR-124 regulates the polarization of microglia to the M2 phenotype by reducing the level of C/EBP-α in the brains of rats with intracerebral hemorrhage. M2-polarized microglia have a protective effect on neuronal injury, thus improving the inflammatory injury induced by ICH. The regulatory mechanism of miR-124 may also be a new therapeutic strategy for treating cerebral hemorrhage (Yu et al., 2017). One recent study illustrated that miR-146a-5p-enriched BMSCs-Exos can offer neuroprotection and functional improvements after ICH by reducing the rates of neuronal apoptosis and inflammation associated with the inhibition of microglial M1 polarization by down-regulating the expressions of IRAK1 and NFAT5 (Duan et al., 2020).

Alzheimer’s disease

Alzheimer’s disease (AD) is a progressive neurodegenerative disease characterized by the aggregation and deposition of Aβ peptides. Clinically, it is characterized by memory impairment, aphasia, apraxia, agnosia, impairment of visuospatial skills, executive dysfunction, and personality and behavioral changes, and has an unknown etiology (Table 6).

**Table 3**  | miRNA expression/function and effect during HIBD
---|---|---|---|---
mRNA | Target | Target trend | Effect | Reference
---|---|---|---|---
miR-592-5p ↑ | PDG2/DP | ↓ | Protect hippocampal neurons from HIBD in neonates | Sun et al., 2018a
miR-17 ↑ | GW0742/PPAR-γ/β/miR-17/TXNIP | ↑ | Attenuate neuronal apoptosis and improve neurological outcomes | Gammadyk et al., 2018
miR-23b/27b ↑ | intrauterine hypoxia | – | Inhibit neuronal apoptosis | Chen et al., 2014
miR-221 ↓ | PUMA/JNK/HHX | ↓ | Reduce neuronal apoptosis | Zhou et al., 2020
miR-146b-5p ↑ | IRAK1/TRAF6/TAK1/NF-κB | ↓ | Alleviate HIE-induced neuron injury and inhibit OGD-induced PC12 cell injury, inflammatory responses, and oxidative stress | Yang and Zhao, 2020
miR-199a-3p ↓ | mTOR | ↑ | Inhibit ischemic injury in peritumoral neurons | Zhao et al., 2020
miR-185-5p ↓ | V4/igf/b3 | ↑ | Promote neuron survival and neurite growth, and suppress cell apoptosis, then further improve motor and cognitive deficits in rats with HIE | Xiong et al., 2020
miR-21a-5p ↑ | Timp3 | ↑ | Attenuate neuronal apoptosis and neuroinflammation | Xin et al., 2020
miR-200b-3p ↓ | Sirt2 | ↑ | Decrease the number of apoptotic neurons and attenuate spatial and learning memory loss | Zhang et al., 2020c
miR-410-3p ↑ | – | – | Promote neuronal survival and inhibit neuronal apoptosis to alleviate the motor, learning, and memory dysfunction caused by HIBD | Xiao et al., 2020
miR-21 ↑ | CCL3 | ↓ | Reduce cerebral infarct volume and the degree of brain tissue damage and improve neurobehavioral ability and memory ability in rats with HIBD | Liu et al., 2020a

**Table 4**  | miRNA expression/function and effect during OGD/R-induced injury
---|---|---|---|---
mRNA | Target | Target trend | Effect | Reference
---|---|---|---|---
miR-181a ↓ | XIAP | ↑ | Protect hippocampal neurons from HIBD in neonates | Zhang et al., 2019c
miR-135b-5p ↑ | GSK-3β | ↑ | Protect neurons against OGD/R-induced injury | Duan et al., 2018
miR-153 ↓ | Nr2f/HO-1 | ↑ | Protect neurons against OGD/R-induced injury | Ji et al., 2017
miR-133b ↑ | IL-1α/IL-6/TNF-α/ELAV1/NLRP3/ caspase-1/J-1 | ↑ | Slow down the pyroptosis of brain neurons in newborn rats of the neuronal oxygen-glucose-deficiency and reoxygenation cell model | Liu et al., 2020b
miR-181a ↓ | LDH | ↓ | Enhance cell viability and reduce apoptosis | Ouyang et al., 2012; Xu et al., 2015
miR-223 ↓ | FGDS-AS1/IGF1R | ↑ | Extenuate OGD/R damage and increase neuron proliferation and reduce neuron apoptosis | Zhang et al., 2017b
miR-142-5p ↑ | Nr2f/ARE | ↑ | Attenuate OGD/R-induced neuron injury | Wang et al., 2017b
miR-182-5p ↑ | SNHG14 | ↑ | Repress apoptosis and reduce OGD/R-induced neuron injury | Deng et al., 2020
miR-29a-3p ↑ | TNFRSF1A/NF-κB | ↓ | Enhance the viability of neurons, obstruct the LDH activity, and reduce apoptosis after OGD/R treatment | Gao et al., 2020
miR-129a ↓ | Cav-1 | ↑ | Protect neurons by attenuating apoptosis | Yue et al., 2019
miR-15a ↓ | BDNF/Pi3K/Akt | ↓ | Inhibit neuronal cell growth and promote neuronal cell apoptosis | Hu et al., 2020
miR-153-3p ↑ | KCNQ1OT1/Fox3 | ↓ | Weaken OGD/R-induced neuronal injury | Wang et al., 2020a

ARE: Antioxidant response element; BDNF: brain-derived neurotrophic factor; GSK-3β: glycogen synthase kinase-3β; HO-1: heme oxygenase-1; IL: interleukin; NF2: nuclear factor erythroid 2-related factor 2; LDH: lactate dehydrogenase; NF-κB: nuclear factor kappa B; OGD/R: oxygen-glucose deprivation and reoxygenation; Pi3K: phosphatidylinositol 3-kinase; TNF: tumor necrosis factor; XIAP: X-linked inhibitor of apoptosis protein.
A study by Zhang et al. (2016b) demonstrated that miR-135b plays a neuroprotective role through the direct targeting of BACE1, and thus may be used for the treatment of AD. Melatonin can protect primary neurons against amyloid-β (Aβ)-induced neurotoxicity in case with AD via the miR-132/PTEN/AKT/FOXO3a pathway, elevate the expression of miR-132, downregulate the expressions of PTEN and FOXO3a during Aβ25-35 exposure, increase the level of p-Akt, and block the nuclear translocation of FOXO3a. The inhibition of the PI3K-Akt pathway can block the protective effects of melatonin, and either the overexpression of miR-132 or the inhibition of PTEN can counteract Aβ-induced neurotoxicity (Zhang et al., 2018). miR-20c plays a corresponding role in the intracellular fixation of neurons in patients with AD, mainly supporting the survival and differentiation of neurons. In the early stage of Aβ injury, the ER stress-induced upregulation of miR-20c inhibits PTEN expression and protects neurons from β toxicity (Wu et al., 2016). In the relevant procedure, miR-132 is a major protective regulator of the growth and development of nerve cells, suggesting that miR-132 supplementation may play a protective regulatory role in the treatment of Tau-related neurodegenerative diseases. miR-132 protects primitive mouse and human wild-type neurons as well as more vulnerable Tau mutant neurons from Aβ and glutamate excitotoxicity (El Fatimy et al., 2018). A study has shown that Grg1 + AGR suppresses the apoptosis of neuronal cells by regulating the expressions of miR-873-5p and downregulating that of HMOX1/Aβ in the case of AD (Shi et al., 2018).

A study by Li et al. (2020a) revealed that miR-338-5p is a protective regulator of the development and progression of AD, and can reduce neuronal apoptosis in APP/P51 mice. The deposition of amyloid plaque and cognitive dysfunction were reduced in APP/P51 mice by the intrahippocampal injection of the lentiviral overexpression of miR-338-5p, which may be related to the negative regulation of BCL2L11 by miR-338-5p (Li et al., 2020a). SOX21-A51 inhibition attenuates Aβ1-40-induced neuronal damage by sponging miR-107, which provides a strategy for the treatment of AD (Xu et al., 2020). Berberine can inhibit caspase-3 activity and apoptosis and is thus an effective drug for the treatment of AD patients. The protective effect of berberine in inhibiting neuronal apoptosis is realized by promoting cell viability through the miR-183-5p/NOS1 pathway (Chen et al., 2020). miR-129 promotes neuronal survival in an in vitro cell model by targeting NR1 and the miR-193-3p/NR1 axis is a potential therapeutic target and promising biomarker for the treatment of AD (Sun et al., 2020a). Tian et al. (2021) showed that miR-20b-5p can disturb the progression of AD by regulating cell apoptosis, cleaved caspase-3 expression, and cell viability by targeting the RhoC gene. This indicates that miR-20b-5p might be an underlying curative target for AD. However, the disadvantage of this study was that only PC12 cells were used to examine the mechanism. More adequate experiments on animals can be performed, along with research involving several other cell lines and clinical samples (Tian et al., 2021). Dex also stimulates pro-apoptotic signaling, although it suppresses the Aβ-induced apoptosis of neuronal cells. miRNA-151-3p enhances the neuroprotective effect of Dex against Aβ by targeting DAPK-1 and TP53 (Guo et al., 2021). Sun et al. (2020b) showed that the miR-129/YAP1/JAG1 axis may be the protective mechanism of demethylated against cognitive dysfunction in AD mice. Dex can enhance the expression of miR-129 in Aβ1-40 mice, and thus can affect the target gene YAP1 that cannot interact with the downstream gene JAG1. This reduces the apoptosis of hippocampal neurons in mice injected with Aβ1-40, and thus, cognitive dysfunction.

**Epilepsy**

Epilepsy is a common disease of the nervous system, the pathogenesis of which is mainly related to the abnormal synchronization of neuronal discharges in the brain (De et al., 2016). The recurrent seizures of epilepsy cause great harm to the physical and mental health of patients. However, the pathogenesis of epilepsy is not fully understood and may be related to the structural and functional damage to the hippocampus and limbic system caused by pathological changes, such as neuronal apoptosis, mossy fiber germination, and synaptic plasticity (Peng et al., 2015). Epileptic seizures can lead to neuronal apoptosis, the mechanism of which can be attributed to the production of a large number of free radicals and the activation of protease related to cell death after epilepsy (Schröder et al., 2014, Table 7).

Anti-miRNA-141 protects against epilepsy-induced apoptosis by upregulating the expression of the SIRT1 protein and suppressing that of the p53 protein (Liu et al., 2019a). Morris et al. (2018) revealed that cholesterol-labeled antibodies targeting miRNA-134 protected against epilepsy by reducing interference with the properties of hippocampal neuronal or the network function. The upregulation of the long non-coding RNA H19 can induce neuronal apoptosis during the latency of epilepsy, and it acts mainly through competition with sponge miRNA let-7b as endogenous RNA to regulate apoptosis. It can be concluded that maintaining a balance between H19 and the sponge miRNA let-7b can help regulate apoptosis and play a corresponding protective role (Han et al., 2018).

Research has shown that the down-regulation of miR-142-5p through the targeting Mir01 inhibits neuronal death and mitochondrial dysfunction, which in turn attenuates the pilocarpine-induced SE. This suggests the potential involvement of miR-142-5p in the pathogenesis of temporal lobe epilepsy (Zhang et al., 2020a). miR-183 has been found to act as a protective regulator in the process of hippocampal neuronal injury and the progression of epilepsy. Inhibited miR-183 can upregulate FoxP1, render the Jak/Stat signaling pathway inactive, promote the proliferation of neurons, and inhibit the apoptosis of hippocampal neurons in epileptic rats (Feng et al., 2019). Knocking down circ_0003170 ameliorates injury to neurons of the human hippocampus that are free of Mg2+ by mediating the miR-421- CCL2 axis (Chen et al., 2021). A study by Li et al. (2020b) revealed that miR-15a-5p was downregulated in children with temporal lobe epilepsy, and the overexpression of miR-15a-5p promoted the viability and inhibited the apoptosis of hippocampal cells. miR-15a-5p might thus be a promising biomarker for the diagnosis of temporal lobe epilepsy in children.
Parkinson’s disease
Parkinson’s disease (PD), which is the second most common progressive neurodegenerative disease worldwide, is characterized by the aggregation of α-synuclein neuronal inclusions and a massive loss of dopaminergic (DA) neurons (Drui et al., 2014; Nussbaum et al., 2017; Chen et al., 2022). The programmed death of dopamine neurons is the main reason for neurodegenerative diseases such as PD (Vila and Przedborski, 2003). In some neurodegenerative diseases including PD, the selective loss of neurons in the dense region of the substantia nigra can negatively affect dopaminergic (mDA) neurons in the ventral tegmental region (Moore et al., 2005). A recent study has demonstrated that miRNAs play a protective role in mDA neuronal differentiation and PD (Harranz et al., 2011; Table 8).

Zhang et al. (2019a) claimed that the inhibition of lnC RNA SNHG14 expression can upregulate a and reduce the accumulation of α-synuclein to alleviate dopaminergic neuronal damage, thereby improving the pathological state of PD, while rotenone may reverse the above-mentioned state by upregulating SNHG14 through SP-1. The extracellular matrix protein laminin-511 (L5M11) binds to integrinα3β1 and activates the transcription cofactor YAP to promote the proliferation and differentiation of mDA neurons. The L5M11-YAP signaling pathway enhances cell survival by inducing the expression of miR-130a, which can inhibit the synthesis of PTEN while increasing the expressions of LMX1A and PTFX3, and preventing the loss of mDA neurons in oxidative stress response (Zhang et al., 2017). miR-212-5p is a neuroprotective regulator in PD, where the overexpression of miR-212-5p can reduce dopaminergic neuronal loss and DAT reduction by targeting SIRT2 (Sun et al., 2018b). The ectopic expression of miR-124-3p was found to attenuate MPP+-induced injury by reducing the expression of TNFR1 in PD model in vitro. The overexpression of neuronal apoptosis, neuroinflammation, and oxidative stress (Geng et al., 2017). The up-regulation of miR-132 expression in the midbrain of rats resulted in a significant decrease in Nurr1 and BDNF levels. It is possible that dopaminergic neurons, which respond to global stress due to the accumulation of α-synuclein, activate miR-132 to shut down Nurr1 and reduce BDNF, a major regulator of neuronal survival. These data highlight that miR-132 is a potential therapeutic target and target for neuroprotective therapy in the case of PD. The development of drugs designed to reduce miR-132 activity may provide a novel strategy for treating PD and other synucleinopathies (Lungu et al., 2013).

In the pathogenesis of PD, the regulation of miR-101-3p expression may play a corresponding role in disease progression. The overexpression of IncRNA-TN196768 reverses the neuronal damage caused by a-synuclein through the down-regulation of miR-101-3p, which can contribute to improving the pathology of PD (Bu et al., 2020). Astaxanthin suppresses ER-induced stress and protects against PD-induced neuronal damage by targeting the miR-3-7/ SHCA axis, suggesting that astaxanthin is a potentially effective therapeutic agent in the treatment of PD (Shen et al., 2021). Bax overexpression reverses the effects of miR-216a on neural cells, and downstream factors are involved in the miR-216a regulation of MPP+-induced neuronal apoptosis. miR-216a regulates the progression of PD by regulating Bax and may be a target for the treatment of PD (Yang et al., 2020b).

Peripheral nervous system injury
Unlike the central nervous system, the peripheral nervous system has a high regenerative capacity after injury, can restore sensory and motor functions, and remains relatively stable throughout a person’s life (Mahar and Cavalli, 2019). Table 9, increasing the expression of miRNAs in exosomes, which are important modulators during peripheral nerve repair derived from sensory neurons, supports the transformation of macrophages into a pro-inflammatory phenotype. These pro-inflammatory macrophages are particularly important for clearing cell debris by phagocytosis and creating a suitable microenvironment for tissue repair (Liu et al., 2019b). Neurons have been shown to secrete an exosome containing miR-132 to endothelial cells, which may promote the angiogenesis of the peripheral nerve and improve vascularization (Liu et al., 2017). López-Leal et al. (2020) observed that miR-21 is upregulated in exosomes derived from repaired Schwann cells to a greater extent than differentiated Schwann cells while regulating the growth of neurites by down-regulating PTEN and activating PI3K. The expression of miR-340 was negatively correlated with the plasmogen activator of its target gene tissue after sciatic nerve injury. The overexpression of miR-340 promotes fibroinlisis, axon regeneration, and the clearance of cell debris (Li et al., 2017).

Role of MiRNAs in Pathology
Neuronal damage caused by chemical/physical factors
Some endogenous and exogenous factors can have positive or negative effects on neurons (Table 10). According to the literature, the overexpression of sevoflurane in the brain may protect against ischemic neuronal injury in vitro (Zita et al., 2010) and in vivo (Chen et al., 2015). In one study, miRNA-132 was downregulated in rats exposed to sevoflurane, and this caused neuronal apoptosis via the suppression of the PI3K/AKT/FOXO3a pathway. This means that the upregulation of miRNA-132 can relieve neuronal apoptosis induced by sevoflurane by undoing the inhibition of the PI3K/AKT/FOXO3a pathway (Dong et al., 2018). The exogenous injection of miR-764 regulates the luteinized-mediated overexpression of NIN2, the expression of which is elevated after nerve injury to promote neurite outgrowth as an adhesion molecule that is expressed in neurons and glial cells (Araki and Milbrandt, 2000). Wang et al. (2017a). It also protects neuronal cells from H2O2-induced cell death and apoptosis (Ding et al., 2018). The upregulation of miR-29b can prevent the apoptosis of mature neurons by directly inhibiting the key step of BH3-only protein induction, which means that reducing the loss of miR-29b expression may have a protective effect on neurons and reverse the occurrence of neurodegeneration (Kole et al., 2011). The upregulation of miR-153 can promote the differentiation of the hippocampal HT-22 cells in mice. It was reported that mouse hippocampal HT-22 cells were cloned from HT4 cells that had no prominently distinct processes or branches (Liu et al., 2009), and protected neurons through the upregulation of the neuronal marker y-enolase, neuronal nuclei, and the functional proteins Snai23, Snai25, and PXS. The main mechanism of differentiation of HT-22 cells induced by the overexpression of miR-153 was one where the numbers of cell processes and branches increased, the distribution of the s-phase of the cell cycle decreased, and the rate of cell proliferation decreased (Xu et al., 2019). The reduced expression of neuronal transcription factor 1α (Nrf1) is associated with the induction of miR-153, which can upregulated anti-apoptotic gene expression and contribute to the pathogenesis of neurodegeneration (Harraz et al., 2011; Table 10). According to the literature, the reduced expression of miR-142-5p reverses the neuronal damage caused by α-synuclein through the targeting of PDE4B, which inhibits mTOR signaling. The enter of miR-142-5p in microglial exosomes increases from the acute phase to the chronic phase of TBI. The increased miR-124-3p in microgli improves neuronal inflammation and contributes to neurite outgrowth by transferring neurons through exosomes. It can also improve neurological outcomes and inhibit neuroinflammation in TBI mice. These effects of miR-124-3p are realized through the targeting of PDE4B, which inhibits mTOR signaling. Therefore, miR-124-3p is a promising therapeutic target for the management of neuronal inflammation after TBI (Huang et al., 2018).

Research has shown that the activation of the nicotinic acetylcholine receptor with nicotine facilitates cell survival by upregulating miR-132-5p, which in turn upregulates the anti-apoptotic protein Bcl-2. These results indicate that miR-132-5p is a potential therapeutic target for neuroprotection that acts by stimulating the nicotinic acetylcholine receptors (Shrestha et al., 2020). The study by Su et al. (2020a) demonstrated that the miR-124-3p suppression of ErA36 stimulates the phosphorylation of the GSK3β(Tyr216)-Tau axis, hinders cell proliferation, and promotes apoptosis in SH-SYSY neuroblastoma cells. Moreover, the miR-455-5p suppression of ErA36 negatively regulates axonal growth in a manner that is dependent on the activity of the GSK2 kinase. Further research will be beneficial for validating the findings and developing therapeutic strategies targeting the miR-455-5p/ErA36 axis to support neuronal viability and axonal regeneration (Su et al., 2020a). Ji et al. (2020) highlighted that acellular exosomes from neurons promote functional...
Table 8 | miRNA expression/function and effect during PD

| miRNA   | Target                | Target trend | Effect                                                                 | Reference |
|---------|-----------------------|--------------|------------------------------------------------------------------------|-----------|
| miR-133b up | SHH1G14/α-syn | ↓            | Mitigate dopaminergic neuron injury and improve the PD pathological state | Zhang et al., 2019a |
| miR-130a down | LMS11-YAP/LMX1A/PTX3 | ↑            | Enhance cell survival and prevent the loss of midbrain neurons in response to oxidative stress | Zhang et al., 2017 |
| miR-21-5p ↑ | SIRT2        | ↓            | Prevent dopaminergic neuron loss                                        | Sun et al., 2018b |
| miR-124-3p ↑ | STAT3        | ↑            | Suppress neurotoxicity, neuronal apoptosis, neuroinflammation, and oxidative stress | Geng et al., 2017 |
| miR-132 up | Nurrl/BDNF     | ↑            | Enhance neuronal survival                                                | Luengo et al., 2013 |
| miR-101-3p up | IncRNA-T199678 | ↑            | Mitigate α-syn-induced dopaminergic neuronal injury                      | Bu et al., 2020 |
| miR-7 ↓ | SNCA           | ↓            | Suppress endoplasmic reticulum stress and protect against PD-caused neuronal damage | Shen et al., 2021 |
| miR-216a ↑ | Bax           | ↓            | Inhibit MPP-induced neuronal apoptosis                                   | Yang et al., 2020b |

BDNF: Brain-derived neurotrophic factor; LMS11: laminin-511; MPP+: 1-methyl-4-phenylpyridinium; PD: Parkinson’s disease; SIRT: sirtuin; STAT3: signal transducer and activator of transcription 3.

Table 9 | miRNA expression/function and effect during peripheral nervous system injury

| miRNA   | Target                | Target trend | Effect                                                                 | Reference |
|---------|-----------------------|--------------|------------------------------------------------------------------------|-----------|
| miR-21-5p ↑ | Macrophages   | ↑            | Clear cell debris after nerve injury and provide a suitable microenvironment for tissue repair | Liu et al., 2019b |
| miR-132 ↑ | Endothelial cells | ↑            | Promote peripheral nerve angiogenesis and improve vascular integrity     | Xu et al., 2017 |
| miR-21 ↑ | PTEN          | ↑            | Regulate the growth promotion of neurite                                | López-Leal, 2020 |
| miR-340 ↑ | tPA           | ↓            | Promote fibrolysis, axon regeneration, and clearance of cell debris     | Li et al., 2017 |

miRNA: MicroRNA; PI3K: phosphatidylinositol 3-kinase; PTEN: phosphatase and tensin homolog deleted on chromosome 10; tPA: tissue plasminogen activator.

Table 10 | miRNA expression/function and effect during neuronal damage caused by chemical/physical factors

| miRNA   | Target                | Target trend | Effect                                                                 | Reference |
|---------|-----------------------|--------------|------------------------------------------------------------------------|-----------|
| miR-132 ↑ | PI3K/AKT/FOXO3a      | ↓            | Relieve neuronal apoptosis                                              | Dong et al., 2018 |
| miR-29b up | BHC-3-only protein  | ↓            | Block apoptosis in mature neurons and expandize long-term neuronal survival | Kole et al., 2011 |
| miR-153 ↑ | SnaP23/SnaP5/Prx5    | ↑            | Protect neural cells and reduce the cell proliferation rate            | Xu et al., 2019 |
| miR-16-199a ↑ | IL-10 | ↑            | Increase cell viability; reduce pro-inflammatory cytokine levels; increase anti-inflammatory cytokine levels; promote cell migration; and reduce the number of cells undergoing apoptosis | Song et al., 2016 |
| miR-212-5p ↑ | Ptg2         | ↓            | Protect against ferroptotic neuronal death in controlled cortical impact mice | Xiao et al., 2019 |
| miR-132-5p ↑ | Bcl-2        | ↑            | Delay neuronal loss and decrease the disease burden                   | Shrestha et al., 2020 |
| miR-455-5p ↑ | ERx36/GSK3B/Tau | ↑            | Promote axonal growth and regeneration and regulate mammalian neuronal viability | Su et al., 2020a |
| miR-124-3p ↑ | PI3K/Akt    | ↓            | Suppress the activation of M1 microglia and microglial-induced neuronal apoptosis to suppress A1 astocytes | Jiang et al., 2020 |
| miR-26a ↑ | GSK3B       | ↑            | Regulate both neuronal polarity and axon growth                        | Lucchi et al., 2020 |
| miR-26a-5p ↑ | sEVs       | ↑            | Impact the development of newborn neurons                             | Luarte et al., 2020 |
| miR-7a ↑ | NF-kB       | ↑            | Alleviate the injury-induced oxidative stress and inhibit apoptosis and rescue neurons and maintain the neural structure | Ding et al., 2020 |
| miR-93 ↓ | MAPK1       | ↑            | Enhance the viability and proliferative ability, as well as reduce apoptosis in morphine-induced HT-22 cells | Wang et al., 2020d |
| miR-181-5p ↓ | TLR4/MyD88/NF-kB | ↑            | Regulate the growth promotion of neurite                               | Wang et al., 2020a |
| miR-223-3p ↓ | Rab1         | ↑            | Alleviate neuropathic pain by inhibiting neuronal autophagy            | Zou et al., 2021 |
| miR-9 ↑ | JNK/NF-kB   | ↓            | Attenuate the loss of viability, stimulation of apoptosis, and release of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) evoked by LPS | Jiang and Wang, 2020 |
| miR-132 ↓ | GATA2/BDNF/SNCA | ↑            | Protect dopaminergic neurons                                            | Nair et al., 2021 |
| miR-862-5p ↓ | Shp1         | ↑            | Protect neuronal cells from MPP+-induced cell death                    | Xue et al., 2020 |
| miR-126 ↓ | p38/MAPK/JNK | ↑            | Reduce neuronal apoptosis of the hippocampus in rats after cardiopulmonary resuscitation | Pan et al., 2020 |
| miR-124/miR-21-5p ↑ | –             | –            | Improve the cell proliferation ability of MSCs and promote the differentiation of MSCs into neurons | Liu et al., 2020d |
| miR-123-3p ↓ | PDE4B       | ↑            | Inhibit neuronal inflammation and contribute to neurite outgrowth       | Huang et al., 2018 |
| miR-92a up | KHC73        | ↓            | Suppress the consolidation of memories                                  | Guven-Ozkan et al., 2020 |
| miR-375 ↓ | CkI           | ↓            | Modulate the circadian rhythm and sleep via targeting ischemic neurons | Xia et al., 2020 |
| miR-23a-3p ↓ | p53/Bcl-2/PUMA/Noxa/Bax | ↓            | Increase neuronal survival upon irradiation                             | Sabirzhanov et al., 2020a |
| miR-211 ↓ | Akt-Gar1/Rad50/Rad54/2i | ↑            | Reduce intrinsic apoptosis following neuronal irradiation              | Sabirzhanov et al., 2020b |
| miR-223 ↓ | NLRP3       | ↑            | Alleviate spinal injury to some extent, reduce pain, and improve nervous system function | Zhang et al., 2020b |
| miR-9-5p ↑ | Pch1-1/Hedgehog | ↑            | Promote angiogenesis and improve neurological functional recovery after TBI | Wu et al., 2020 |
| miR-124 ↑ | RARG        | ↑            | Stimulate neurite growth in N2a cells and primary neurons              | Su et al., 2020b |
| miR-133a ↑ | Gm15621/Socx4 | ↑            | Reduce the apoptosis and cell survival rates and attenuate inflammation | Zhao and Ai, 2020 |
| miR-24 ↑ | p27Kip1     | ↑            | Inhibit oxidative damage and neuronal apoptosis in the hippocampus and the size and Ca2+ permeability of the mitochondria of hippocampal neurons | Li et al., 2020c |
| miR-429 ↓ | BAG5        | ↑            | Attenuate ketamine-induced neurotoxicity in PC12 cells                | Fan et al., 2021 |
| miR-29a ↓ | Fln1/Fstl1/Lam2c | ↓            | Regulate the growth promotion of neurite                               | Huang et al., 2018 |

BDNF: Brain-derived neurotrophic factor; ERK1/2: extracellular signal-regulated kinase 1 and 2; Fln1: Fibrinllin 1; FoxO: forkhead transcription factor O subfamily; Fstl1: follistatin-like 1; GSK-3β: glycogen synthase kinase-3β; IL: interleukin; JNK: c-Jun N-terminal; Lamc2: laminin subunit gamma 2; MAPK: mitogen-activated protein kinases; miRNA: microRNA; mTOR: mammalian target of rapamycin; MyD88: myeloid differentiation factor 8β; NF-kB: nuclear factor-kB; NLRP3: NLR family pyrin domain containing 3; NSC: neural stem cell; PDE4B: phosphatidylinositol 3-kinase; PI3K: phosphatidylinositol 3-kinase; PUMA: p53-upregulated mediator of apoptosis; RARG: retinoic acid receptor gamma; sEVs: small extracellular vesicles; TLR: Toll-like receptor; TNF-α: tumor necrosis factor α; TRAF: TNF receptor-associated factor; XIAP: X-linked inhibitor of apoptosis protein.
behavioral recovery by shutting miR-124-3p in mouse spinal cord injury (SCI). The enriched levels of exosomal miR-124-3p improved therapeutic potential by suppressing the activation of M1 microglia, thus reducing neuroinflammation to suppress A1 astrocytes, and by the MYYH/PISK/AKT/ 
NF-κB signaling pathway. A combination of miRNAs and neuron-derived exosomes may be a promising and minimally invasive approach to the treatment of spinal cord injuries (Jiang et al., 2020). miR-26a, at a junction of regulatory mechanisms, impinges on neuronal survival and axon development via the control of GSK3β levels. In this context, the relatively high levels of miR-26a expression in mature neuronal cultures and the central nervous system raise questions about its role in the adult brain. These results demonstrate how axonal miR-26a can regulate local protein translation in the axon to facilitate retrograde communication to the soma, and to amplify neuronal responses in a mechanism that influences axon development (Lucci et al., 2020). Luarte et al. (2020) supported a novel and complex level of astrocyte-to-neuron communication that is mediated by astrocyte-derived small EVs and the activity of their miRNA content. Their study suggests that astrocytes can regulate the dendritic development of neurons by modulating the miRNA cargo of small EVs derived from them (Luarte et al., 2020). The upregulation of miR-7a alleviates injury-induced oxidative stress and inhibits apoptosis by down-regulating the NF-κB pathway in rats with spinal cord injury. In addition, the upregulation of miR-7a can rescue neurons and maintain their neural structure (Ding et al., 2020). Acupuncture attenuates cognitive impairment associated with inflammation by inhibiting the miR-39-mediated TLR4/MYD88/NF-κB signaling pathway in the case of vascular dementia. Acupuncture serves as a promising alternative therapy, and may be an underlying TLR4 inhibitor for the treatment of vascular dementia. Recent work provides a new perspective on the anti-inflammatory mechanism of acupuncture and identifies it as a potential complementary therapy for cognitive dysfunction (Wang et al., 2020d). Morphine induces the apoptosis of hippocampal HT-22 neurons by upregulating miR-181-5p to suppress the level of MAPK1. MiR-181-5p may be a therapeutic target in the future (Wang et al., 2020e). By increasing miR-223-3p expression while targeting Rab1, electroacupuncture reduces neuronal apoptosis (neuronal autophagy as the form of death) and inflammation, and increases the threshold of rats with PHN for mechanical pain (Zou et al., 2021). The neuroprotective effect of matrine may protect PC12 cells in vitro from LPS-induced damage by regulating miR-9 expression, and targeting its downstream JNK and NF-κB pathways (Ji et al., 2020). The innate ability of humans to appreciate music induces a corresponding miRNA response. miR-132 and Dicer are upregulated when one listens to music, followed by the targeting of the music predisposition regulator GATA2, and BDNF and SNCA are then activated. They are also the preferred candidate genes for musical talents, thereby protecting dopaminergic neurons that are important for maintaining striatum dopamine levels (Nair et al., 2021). Pan et al. (2020) reported that miR-126 can significantly reduce neuronal apoptosis in the hippocampus and improve the neurological function in rats after cardiopulmonary resuscitation, where this miRNA may be used as a potential therapeutic target. The injection of miR-6862 upregulates its target gene SphK1 and then protects nerve cells from MPP+-induced damage, thereby protecting DA neurons from oxidative damage (Xue et al., 2020). The inhibition of miR-92a expression enhances the expression of a specific kinesin molecule, the kinesin heavy chain 73 (KHC73), in neurons of the brain of drosophila to enhance expression enhances the expression of a specific kinesin molecule, the kinesin heavy chain 73 (KHC73), in neurons of the brain of drosophila to enhance expression enhances the expression of a specific kinesin molecule, the kinesin heavy chain 73 (KHC73), in neurons of the brain of drosophila to enhance expression enhances the expression of a specific kinesin molecule, the kinesin heavy chain 73 (KHC73), in neurons of the brain of drosophila to enhance expression enhances the expression of a specific kinesin molecule, the kinesin heavy chain 73 (KHC73), in neurons of the brain of drosophila to enhance expression enhances the expression of a specific kinesin molecule, the kinesin heavy chain 73 (KHC73), in neurons of the brain of drosophila to enhance.
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