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REVIEW

Non-coding RNAs as Emerging Regulators of Neural Injury Responses and Regeneration

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Abstract Non-coding RNAs (ncRNAs) are a large cluster of RNAs that do not encode proteins, but have multiple functions in diverse cellular processes. Mounting evidence indicates the involvement of ncRNAs in the physiology and pathophysiology of the central and peripheral nervous systems. It has been shown that numerous ncRNAs, especially microRNAs and long non-coding RNAs, are differentially expressed after insults such as acquired brain injury, spinal cord injury, and peripheral nerve injury. These ncRNAs affect neuronal survival, neurite regrowth, and glial phenotype primarily by targeting specific mRNAs, resulting in translation repression or degradation of the mRNAs. An increasing number of studies have investigated the regulatory roles of microRNAs and long non-coding RNAs in neural injury and regeneration, and thus a new research field is emerging. In this review, we highlight current progress in the field in an attempt to provide further insight into post-transcriptional changes occurring after neural injury, and to facilitate the potential use of ncRNAs for improving neural regeneration. We also suggest potential directions for future studies.

Keywords ncRNA · miRNA · lncRNA · Nerve injury · Regeneration

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Introduction

In clinical practice, injuries to the central and peripheral nervous systems (CNS and PNS) are commonly encountered. Injured CNS neurons are unable to regenerate their axons spontaneously because of suppression by glial scar-associated inhibitors and myelin-derived molecules as well as loss of the capacity for developmentally regulated intrinsic growth [1, 2]. In contrast, PNS neurons show a robust intrinsic regenerative capacity after traumatic injury, but functional outcomes are often unsatisfactory [3]. Accordingly, much research has been devoted to the development of therapeutic interventions to improve neural regeneration based on an understanding of the molecular mechanisms underlying the responses to injury and regeneration.

To initiate a regenerative response, the PNS neuron must shift from a transmitting state to a regenerative state, which requires the initiation of a growth program through gene transcription and the activation of local signaling cascades that control axon assembly. Knowledge of the gene transcription responses of PNS neurons to injury has provided insight into the genes associated with regeneration. Many regeneration-associated genes have been identified by examining gene expression changes after injury. These genes include transcription factors, such as ATF3, c-Jun, C/EBPb, CREB, NFIL3, p53, SMAD1, SOX11, STAT3, and KLF family members, while non-transcription factor "terminal" genes consist of those that encode adhesion/guidance molecules (integrin subunits and CD44), neuropeptides (VIP and CGRP), structural and cytoskeleton-associated proteins (GAP43, CAP23, SCG10, and CRMP2), and metabolic enzymes (arginase 1) [4]. In addition to increasing RAG expression, another approach to enhancing regeneration is to increase the "metabolic

growth state" of neurons by up-regulating anabolic processes, such as mTOR activation of protein translation or transcriptional regulation of anabolic processes [5, 6].

Clearly, the molecular approaches to neural regeneration noted above are mainly based on transcriptional regulation. Recently, many studies on non-coding RNAs (ncRNAs) have revealed an emerging layer of post-transcriptional gene regulation for the post-neural-injury process. ncRNAs are a large cluster of RNAs that are not translated into proteins. As the sequencing of the human genome reported the surprising finding that about 20,000 protein-coding genes represent <2% of the total genomic sequence, the investigation of ncRNAs has attracted increasing attention because they have multiple functions at the transcriptional and post-transcriptional levels in diverse cellular processes [7].

Recently, a number of studies have shown that ncRNAs, mainly microRNAs and long ncRNAs, are differentially expressed in injured neural tissue after various types of injury. Dysregulation of ncRNA expression affects the survival and growth of neurons and regulates the phenotypic modulation of glial cells. These intriguing results contribute to the potential use of ncRNAs as diagnostic markers and therapeutic targets for neural injury. This review aims to summarize current research progress in understanding the involvement of ncRNAs in CNS and PNS injury and the effects of ncRNAs on neural regeneration. We also suggest potential directions for future research.

Classification of Non-coding RNAs

The ncRNAs have a high degree of heterogeneity in sequence, structure, and biological function. They are usually classified into subtypes according to various criteria. For instance, ncRNAs are divided into housekeeping and regulatory types according to their biological functions. The former includes ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), guide RNAs (gRNAs) and telomerase RNAs, while the latter includes microRNAs (miRNAs, miRs), small interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), and long chain non-coding RNAs (long non-coding RNAs, lncRNAs). Also, ncRNAs are divided into nuclear and cytoplasmic types according to subcellular localization, or divided into those with a polyA tail (polyA-plus ncRNAs) and those without (polyA-minus ncRNAs). In addition, ncRNAs are divided into short and long types according to the length of the transcript. The short type includes miRNAs, siRNAs, piRNAs, snRNAs, and snoRNAs [8], which are <200 nucleotides (nt) long, typically 20–30 nt, while the long type (lncRNAs) are >200 nt in length, and account for at least 80% of mammalian genome transcription [9].

In this review, we focus on two members of the ncRNA family to describe the regulation of neural regeneration by miRNAs at the post-transcriptional level and by lncRNAs at both the transcriptional and post-transcriptional levels [10].

miRNAs are a class of endogenous small single-strand ncRNAs of about 22 nt. They have been widely investigated since the first miRNA (lin-4) was identified. They are generated by RNA polymerase II, and their encoding sequence is often found in an intergenic region in the form of a single copy, multiple copies, or a gene cluster, while the encoding sequences of other miRNAs occur in the exon or intron regions of a gene. Mature miRNAs combine with Argonaute 1 to form an RNA-induced silencing complex (RISC) that is involved in the regulation of cellular life [11]. Put simply, the RISC influences the stability and translation of messenger RNA (mRNA) through direct effects on the 3′-untranslated region of the target mRNA, thereby resulting in translation repression or degradation of the mRNA. Importantly, miRNAs are abundant in the nervous system where they function in development [12] and maintenance of the neuronal phenotype [13], influence the maturation of dendrites and spines [14], and serve as effectors of synaptic plasticity and function [15, 16]. Lack of a specific miRNA, miRNA overexpression, or miRNA mutation may lead to abnormal cellular function and even neurological disorders [17].

lncRNAs are >200 nt in length but lack open reading frames. They can be classified on the basis of genomic location and biogenesis into (1) sense lncRNAs that are transcribed on the same strand of an exon; (2) antisense lncRNAs that are transcribed on the opposite strand of an exon; (3) bidirectional lncRNAs that are located on the opposite strand from a protein-coding gene whose transcription is initiated <1000 bp away; (4) intronic lncRNAs; (5) intergenic lncRNAs (also called long intergenic non-coding RNAs, lincRNAs) that occur between two genes; and (6) circular RNAs with exonic or intronic linear sequences that circularize after alternative splicing [18, 19]. lncRNAs were once considered to be intermediate products in the transcription process, and to have no biological functions. Nowadays, however, increasing evidence has shown that lncRNAs have complex functions, including activation or reduction of the expression of specific genes, especially adjacent protein-encoding genes, and are associated with the pathogenesis of some diseases.

Roles of miRNAs in Responses to Neural Injury

During neurogenesis, neuronal maturation, and brain development, miRNAs serve as fine regulators of genetic networks [20]. For the development and maintenance of

neurons, miRNAs play roles in cell specification, axonal path-finding, and apoptosis [21, 22]. It is important to determine the dysregulation of miRNAs during neurodevelopmental abnormalities and neurodegenerative disorders such as fragile X syndrome, autism spectrum disorder, Rett syndrome, depression, drug addiction, Huntington's disease, and schizophrenia [23–26]. Here, however, we focus on the involvement of miRNAs in the responses to various types of neural injury.

miRNAs in Acquired Brain Injury

Acquired brain injury (ABI) is defined as an injury to the brain occurring after birth. It is not a hereditary, congenital, or degenerative disease [27, 28], but is caused by stroke, hemorrhage, infection, or trauma. Several miRNAs, such as miR-9, miR-183, miR-134, miR-135, miR-124a, miR-124b, miR-153, and miR-219, are highly enriched and specifically located in the brain [29, 30]. The expression of miR-146b, miR-551b, miR-92b, and miR-384 is several-fold higher in the hippocampus than in the cortex [31]; miR-132, miR-212, miR-221, miR-222, and let-7 are predominantly expressed in forebrain regions; and miR-206 and miR-497 are mainly expressed in the cerebellum. This region-specific expression of miRNAs in the brain suggests that they play specific regulatory roles in ABI [32].

Ischemic Brain Injury

Stroke is a major cause of serious long-term disability after focal cerebral ischemic injury. Microarray data on a large scale has identified the miRNA expression profiles after middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia. It has been shown that 12 miRNAs are up-regulated and 18 are down-regulated in the infarct region after 6 h of MCAO [33]. The serum miR-126 levels appear to differ in permanent *versus* transient ischemia, and the changes in these levels may be used to distinguish severe permanent ischemia from transient ischemia [34].

miRNAs can regulate the ischemic brain injury caused by a thrombus, embolus, or other interruption of the arterial supply [35, 36]. Expression of the glutamate receptor subunits GluR2 and NR2B, together with *N*-methyl-D-aspartate receptor-mediated Ca^{2+} influx, is inhibited by the overexpression of miR-223, thereby protecting neurons from cell death [37]. Administration of anti-miR-320a leads to a reduction of infarct volume as well as an increase in the expression of aquaporins 1 and 4 after cerebral ischemia [38]. The expression of let-7c-5p is decreased in the plasma of patients with ischemic stroke, but its overexpression suppresses microglia activation against ischemic damage [39].

After ischemic brain injury, neuronal death is one of the most important events that influences recovery, and miRNAs regulate neuronal survival. Two key regulator of apoptosis, B cell lymphoma 2 (Bcl-2) and Bcl-w, are regulated by miR-15b [40], miR-29b [41], miR-181a [42], and miR-497 [43]. miR-181c suppresses the expression of tumor necrosis factor-α (a key pro-inflammatory cytokine) to protect neurons from cell death [44]. miR-592 decreases the expression of $p75^{NTR}$, an ischemia-induced neurotrophin receptor, attenuates the activation of pro-apoptotic signaling pathways, and prevents neuronal apoptosis [45]. miR-134 down-regulates the expression of heat shock protein A12B (HSPA12B) and promotes neuronal death after ischemic injury [46].

After transient cerebral ischemia, miR-200c expression in the brain increases rapidly, contributing to cell death by inhibiting Reelin expression [47]. Down-regulation of miR-30a expression prevents neuronal ischemic injury by up-regulating the expression of HSPA5, while decreased endoplasmic reticulum stress-induced apoptosis might be one of the mechanisms underlying HSPA5-mediated neuroprotection [48, 49].

miR-424 and miR-23a-3p inhibit neuronal apoptosis after ischemia, reduce the levels of reactive oxygen species in cortex, and abrogate H_2O_2-induced injury by increasing cellular viability and manganese superoxide dismutase activity [50, 51]. miR-134 regulates ischemic/reperfusion injury-induced neuronal death via CREB (cAMP response element-binding protein) signaling [46, 52]. miR-22 inhibits nuclear factor-κB activity by decreasing the nuclear receptor coactivator 1 expression and caspase-3 activity and thus reduces cortical neuronal apoptosis [53]. miR-23a/b and miR-27a/b suppress Apaf-1 (apoptotic protease activating factor 1) protein and alleviate the neuronal apoptosis induced by intrauterine hypoxia [54]. miR-124 targets Ku70 to improve ischemia/reperfusion-induced brain injury and dysfunction [55].

Collectively, the above findings confirm that miRNAs are key regulators of neuronal cell death. As potential targets for promoting neuronal survival, miRNAs contribute to recovery after ischemic brain injury.

Traumatic Brain Injury

In contrast to ischemic brain injury that generally occurs in the older population, traumatic brain injury (TBI) is a leading cause of death, disability, and cognitive impairment in children and young adults.

Microarray analysis has shown that many miRNAs exhibit differential expressions after TBI. Since TBI is attenuated by hypothermia, it may be linked to the temperature-sensitive miRNAs [56–58]. Mitochondria-associated miRNAs, such as miR-155 and miR-223, both of

which play roles in inflammatory processes, are significantly dysregulated in the hippocampus after TBI [59]. Rapid up-regulation of miR-711 following secondary injury after TBI stimulates neuronal death by inhibiting the serine/threonine kinase Akt and activating FoxO3, GSK3α/β, PUMA, and Bim [60]. miR-21 expression changes in response to TBI, inhibits apoptosis, and promotes angiogenesis by down-regulating the expression of apoptosis- and angiogenesis-related molecules and PTEN as well as increasing the phosphorylation of Akt [61, 62]. The expression of miR-23a and miR-27a is down-regulated after TBI, thus contributing to neuronal death by up-regulating members of the Bcl-2 family [63].

After injury, the axons of retinal ganglion cells in adult mammals rapidly degenerate and the cell bodies may die, while glial cells at the injury site undergo scar formation. However, miR-30b decreases the sema3A levels to promote axon outgrowth [64]. In zebrafish retina, the miRNA and mRNA expression profiles indicate that miR-29b and miR-223 promote regeneration by regulating key biological processes, including cell survival/apoptosis, extracellular matrix-cytoskeleton signaling, and heparan sulfate proteoglycan binding [65].

miRNAs in Spinal Cord Injury

Spinal cord injury (SCI) is followed by excitotoxicity, edema, inflammation, ischemia, and chronic demyelination as secondary injuries, leading to additional damage [66]. Numerous miRNAs are highly expressed and localized in the spinal cord as well as in the brain. In adult rats, >77% of the identified mature miRNAs are expressed in the spinal cord [67]. Several, such as miR-1, miR-10a, miR-338, miR-451, miR-34a, miR-133a, miR-133b, miR-142-3p, miR-199, miR-10b, and miR-219 are highly enriched in the spinal cord [21], and their expression changes dynamically after SCI [67, 68]. For example, increased miR-223 expression regulates the expression of early-phase genes after SCI [68]. The expression of miR-124, which controls neurogenesis and neurite outgrowth during differentiation, is down-regulated after SCI [69, 70], and it affects inflammatory nociception by regulating methyl-CpG-binding protein 2 (MeCP2) and inflammation-related genes [71]. Further, miR-124 also targets the transcription factor CEBPα, holding promise as a target for treating neuroinflammation [72]. miR-486 down-regulates neurogenic differentiation 6 (Neurod 6) expression, thus enhancing apoptosis and functional deficits in neurons after SCI [73]. miR-126 targets such genes as SPRED1, PIK3R2, and VCAM1 to rescue tissue damage and to improve the functional deficit; its expression is down-regulated after SCI [74].

Astrocytes, specialized glial cells, perform supportive, metabolic, and homeostatic functions in the CNS [75]. miR-181 is a negative regulator of astrocyte activation, and its expression is down-regulated by inflammatory stimuli. Accordingly, miR-181 affects inflammatory cytokine secretion in astrocytes and modulates astrocyte activation and differentiation by targeting MeCP2 (methyl-CpG-binding protein 2) [44]. Similarly, miR-146a regulates the release of cytokines from astrocytes [76]. miR-17-5p targets the cell-cycle inhibitors P21 and RB1 to promote the proliferation of reactive astrocytes and facilitate functional recovery after SCI [77]. Transfection with miR-124 can improve the outcome of neural stem-cell transplantation in SCI rats by increasing the numbers of neurons and reducing the numbers of GFAP-positive astrocytes [78].

In the spinal cord, motor neuron subtypes are organized into columns that project axons to specific target muscles. For instance, the medial motor columns innervate axial muscles, while the lateral motor columns innervate limb muscles [79, 80]. Specification of the motor columns requires extrinsic signaling pathways to induce sequential Hox transcription-factor-mediated responses [79, 81]. miRNAs participate in the process of motor neuron gene regulation, including development, motor neuron disease, axon regeneration, and synaptic connection. miR-20a causes continuing motor neuron degeneration by down-regulating neurogenin 1 while up-regulation of neurogenin may protect motor neurons from aggressive secondary injury [82]. miR-29b reduces the expression of Bad, Bim, Noxa, and Puma, and plays a role in neuronal apoptosis in SCI. Down-regulation of miR-20a and miR-29b expression may cooperatively protect motor neurons from cell death by down-regulating the Mcl-1 (myeloid cell leukemia 1) and up-regulating BH3-only proteins after SCI [83]. miRNAs are also important for axonal regeneration in spinal motor neurons. After SCI, the elevated expression of miR-133b represses mRNA translation of RhoA, promoting the functional recovery of motor neuron axons [84].

Taken together, miRNAs play regulatory roles in neuronal-subtype specification, functional maintenance, and motor neuron regeneration after SCI.

miRNAs in Peripheral Nerve Injury

After peripheral nerve injury, the regenerating axons in the proximal nerve stump can grow across the lesion due to activation of the intrinsic growth capacity of neurons and the formation of a regenerative microenvironment. De-differentiated Schwann cells replenish lost or damaged tissues by proliferation, and produce a favorable environment for axonal outgrowth by helping to clear myelin debris and forming cellular conduits or corridors that guide axons through the degenerated nerve stump and back to

their targets [85]. A recent study has suggested that knockout of *Dicer* impedes regenerative axon growth as well as anatomical, physiological, and functional recovery. The data suggest that an intact *Dicer*-dependent miRNA pathway is critical for successful peripheral nerve regeneration after injury [86].

Neuronal Survival

The survival of injured neurons is a necessary prerequisite for axonal regrowth. The expression of miR-21 and miR-222 increases continuously in dorsal root ganglia (DRG, L4-L6) during the initial 7-day period after sciatic nerve transection, and tissue inhibitor of metalloproteinase 3 (TIMP3) has been identified as a common target of miR-21 and miR-222. Overexpression of miR-21 and miR-222 reduces apoptosis and enhances the viability of cultured DRG neurons. Interleukin 6 (IL-6) up-regulates the miR-21 expression in these neurons [87]. miR-146a mediates apoptosis in DRG neurons under hyperglycemic conditions, which down-regulate miR-146a expression, improving the protein level of both IL-1 receptor-activated kinase and tumor necrosis factor receptor-associated factor 6 in DRGs [88].

Neurite Outgrowth

Microarray analysis and deep sequencing have revealed that many miRNAs regulate the expression of transcription factors and signaling mediators that are important for peripheral nerve regeneration [86]. In particular, the influences of miRNAs on neurite outgrowth from DRG neurons have been extensively investigated. For example, miR-21 promotes axonal growth from adult DRG neurons by targeting Sprouty2 (a specific inhibitor of the Ras/Raf/ERK pathway) [89], and miR-222 also promotes neurite outgrowth from these neurons by targeting PTEN (phosphatase and tensin homolog deleted on chromosome 10, a negative regulator of Akt) [90]. Several other miRNAs, including miR-8, miR-431, miR-145, and miR-138, have been shown to play regulatory roles in neurite outgrowth. Their targets are the cell-adhesion molecules Fasciclin III (Fas III) and Neuroglian (Nrg), Kremen1 (an antagonist of Wnt/β-catenin signaling), Robo2 (a transmembrane receptor), and Sirtuin type 1 (an NAD-dependent histone deacetylase), respectively [91–94].

Multiple targets of miR-21 have been validated, two-thirds of which are linked to intrinsic and/or extrinsic pathways of apoptosis [95]. miR-21 promotes neurite outgrowth by down-regulating the expression of its target gene, SPRY2142. Moreover, miR-21 expression is up-regulated in DRG neurons after sciatic nerve injury [87] (Fig. 1). After this injury, miR-21 and miR-222 promote neurite outgrowth and inhibit apoptosis by repressing TIMP3 in DRGs, suggesting that the two miRNAs are candidate hub molecules for triggering intrinsic neurite growth in injured DRG neurons [87, 89] (Fig. 1).

miR-132 plays roles in dendrite morphology and synaptic function [96]. Its knockdown reduces axonal extension in cultured DRG neurons while overexpression increases axonal extension. Moreover, miR-132 regulates the mRNA level of RAS p21 protein activator 1 gene, serving as a positive regulator of developing axon extension [97]. miR-26a specifically targets glycogen synthase kinase 3β (GSK3β) to rescue axon regeneration, and the miR-26a-GSK3β pathway regulates axon regeneration at the neuronal soma by controlling the expression of Smad1, a regeneration-associated transcription factor [98]. let-7 inhibits the lin-41 expression in older neurons while lin-41 inhibits the let-7 expression in younger neurons. A let-7-lin-41 regulatory circuit can ensure that axon regeneration is inhibited only in older neurons [99].

Schwann Cell Phenotype Modulation

Evidence has identified a specific cohort of miRNAs as epigenetic regulators of the transition between the differentiation and de-differentiation of Schwann cells during the acute phase of PNS injury. miR-138 and miR-709 show the highest affinity for regulating the expression of Egr2, Sox-2, and c-Jun after PNS injury [100]. miR-204 negatively regulates Nrn1 protein expression and activates cleaved caspase-3, stimulating the apoptosis of Schwann cells after exposure to H_2O_2-induced oxidative stress [101]. miR-182 inhibits the proliferation and migration of Schwann cells by targeting fibroblast growth factor 9 and neurotrimin, respectively, at an early stage following sciatic nerve injury [102]. miR-221 and -222 promote the proliferation and migration of Schwann cells by targeting longevity assurance homologue 2, a suppressor of cell growth and metastasis, which can increase the intracellular H^+ concentration by interacting with V-ATPase [103].

miR-9 is an important functional regulator of Schwann cell migration by directly targeting collagen triple-helix repeat-containing protein 1, which in turn inactivates downstream Rac1 GTPase [104]. let-7 miRNA significantly reduces the proliferation and migration of primary Schwann cells by suppressing the protein translation of nerve growth factor (NGF). The detailed mechanism seems to be that the NGF expression inhibited by let-7 miRNA can regulate the miR-221/222 expression to affect the Schwann cell phenotype [105]. Increased miR-132 expression induced by hypoxia enhances Schwann cell migration and down-regulates the target, PRKAG3, to facilitate peripheral nerve regeneration [106].

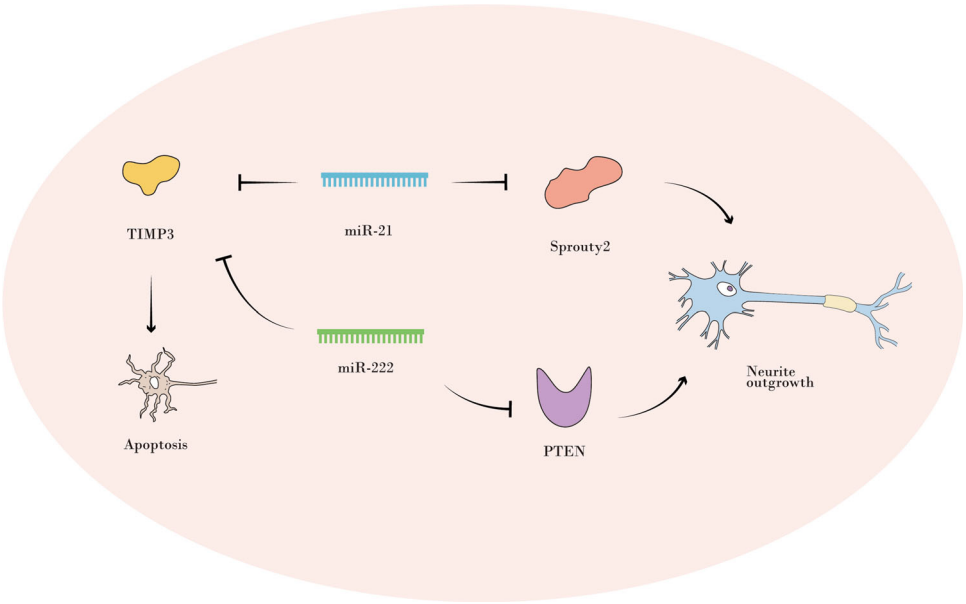

Fig. 1 Schematic diagram illustrating (1) the joint inhibitory effects of miR-21 and miR-222 on neuronal apoptosis through suppressing TIMP3 after peripheral nerve injury, and (2) the promoting effects of miR-21 and miR-222 on neurite regrowth through suppressing sprouty2 and PTEN, respectively, after peripheral nerve injury. *T-shaped lines* indicate an inhibitory effect or negative regulation while arrows indicate a promoting effect.

miR-34a is highly expressed in the adult nervous system, and Notch1 and cyclin D1 are its targets in cancer cells [107]. These two targets are also important mediators of Schwann cell dedifferentiation and proliferation after peripheral nerve injury [108, 109]. miR-140 targets the transcription factor Egr2, a master regulator of myelination, and modulates axonal myelination in co-cultures of DRG neurons and Schwann cells [110]. miR-29a inhibits peripheral myelin protein, which is a dose-sensitive, disease-associated protein primarily expressed in myelinating Schwann cells [111]. The effects of several miRNAs on Schwann cells after peripheral nerve injury are illustrated in Fig. 2.

For the sake of convenience to the reader, we summarize the above description by listing many miRNAs that have been reported to be associated with various injuries to the nervous system and highlighting their functional significance in neural regeneration (Table 1).

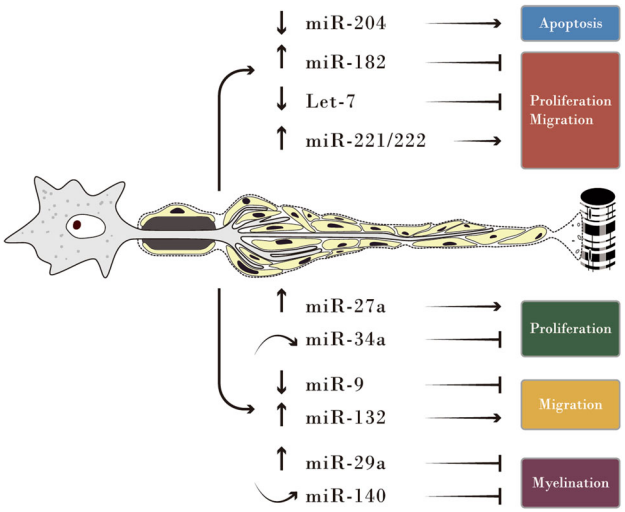

Fig. 2 After peripheral nerve injury, the expression of miR-204, let-7, mir-27a, and miR-29 is constantly down-regulated (*downward arrows*), while that of of miR-182, miR-221/222, miR-27a, and miR-132, and miR-29a is constantly up-regulated (*upward arrows*), and that of of miR-34a and miR-140 is dysregulated (*curved arrows*). After peripheral nerve injury, these miRNAs regulate the behavior of Schwann cells, such as apoptosis, proliferation, migration, and myelination, as indicated by arrows or *T-shaped lines* (positive and negative regulation, respectively). Also shown (*middle*) is a schematic showing the process of axonal regrowth from an injured peripheral neuron while reaching the target organ for re-innervation, coupled with myelination of the re-growing axon by Schwann cells.

Roles of lncRNAs in Responses to Nerve Injury

lncRNAs are specifically expressed in the CNS and PNS, and may be involved in regeneration. To date, several reports have described the roles of lncRNAs in CNS development and neurogenesis [112, 113]. It has been shown that a total of 322 lncRNAs are differentially expressed in the brain with hypoxic-ischemic damage, and silencing of the lncRNA BC088414 decreases apoptosis and increases cell proliferation [114]. These findings suggests the roles of lncRNAs in CNS injury.

In investigations of the impact of lncRNAs on the intrinsic regenerative capacity of peripheral neurons, a total of 105 lncRNAs have been found to show significant differential expression in DRGs after sciatic nerve injury. Among these, BC089918 and uc.217 have been specifically investigated and the results showed that down-regulation of BC089918 expression [115], and silencing of uc.217

Table 1 miRNA regulation of regeneration after injury to the nervous system.

miRNAs	Injury model	Tissues	Times	Expression change	Functions	Refs
Acquired brain injury						
miR-223	NMDA-induced injury, BCCAO/reperfusion in mice	Striatum; hippocampus	7 d	Increased	Inhibiting neuronal cell death	[37]
miR-320a	MCAO/reperfusion in rats	Brain	1 d	Decreased	Promoting neuronal cell death	[38]
Let-7c-5p	Cerebral infarction in male patients, MCAO/reperfusion in mice	Plasma, ipsilateral cortex, striatum	1 h	Decreased	Inhibiting microglia activation	[39]
miR-181c	LPS in mice	Cerebral cortex	4 h	Decreased	Inducing anti-inflammatory cytokines	[44]
miR-592	MCAO/reperfusion; OGD in mice	Brain; hippocampal slices or neurons	4–8 h	Decreased	Inhibiting neuronal cell death and apoptosis	[45]
miR-134	MCAO/reperfusion in mice; OGD	Brain; n2a	1 h	Decreased	Exacerbating cell death and apoptosis	[46]
miR-200c	MCAO/reperfusion in mice	Brain	1, 3, and 24 h	Increased	Promoting neuronal cell death	[47]
miR-30a	OGD/reoxygenation in mouse	Cortical neurons	1 h	Decreased	Promoting neuronal cell death	[48]
miR-30a	MCAO/reperfusion in mice	Peri-infarct region	1 h	Decreased	Promoting neuronal cell death	[49]
miR-424	MCAO/reperfusion in mice; H_2O_2-induced injury	Peri-infarct cortex; primary cortical neurons	1–24 h	Increased and then decreased	Inhibiting neuronal apoptosis	[50]
miR-23a-3p	MCAO/reperfusion in mice	Peri-infarction; infarction core	4 h and 24 h	Increased	Inhibiting neuronal apoptosis	[51]
miR-134	MCAO/reperfusion in mice	Brain	12 h, 1, 3, and 7 d	Increased	Promoting neuronal cell death and apoptosis	[52]
miR-23a/b, miR-27a/b	Hypoxia in mice	Cortical neurons; brain	6–24 h	Decreased	Alleviating hypoxia-induced neuronal apoptosis	[54]
miR-124	MCAO/reperfusion in rats	Brain	24 h	Decreased	Inducing neuronal cell death	[55]
miR-711	CCI in mice	Cortex	3 d	Increased	Inducing neuronal cell death	[60]
miR-21	FPI	Cerebral cortex and ipsilateral hippocampus	1 h, 1, 3, 7, and 14 d	Increased and then declined to baseline	Inhibiting apoptosis and promoting angiogenesis	[61]
miR-23a, miR-27a	CCI in mice; etoposide-induced apoptosis in primary cortical neurons	Cortex; hippocampus	1–72 h	Decreased	Inhibiting neuronal cell death	[63]
miR-30b	ONC in rats	Retina	1, 3, 7, 14, and 21 d	Increased and then declined to baseline	Promoting axon growth	[64]
miR-29b, miR-223	ONC in zebrafish	Retina	3 d	Increased	Inducing cell survival	[65]
Spinal cord injury						
miR-124a	Peripheral noxious stimulation with formalin in mice	Dorsal horn	1, 8, 24, and 48 h	Decreased	Decreasing nociception	[71]
miR-486	SCI in mice	Motor neurons	3 d	Increased	Increasing neuronal death and demyelination	[73]
miR-126	SCI in rats	Spinal cord	1, 3, and 7 d	Secreased	Promoting angiogenesis and attenuating inflammation	[74]
miR-20a	Spinal cord transection in mice	Motor neurons	1, 2, and 3 d	Increased	Inducing apoptotic Neural cell death	[82]
miR-29b	SCI in mice	Spinal cord	6 d	Decreased	Inhibiting neuron apoptosis	[83]

Table 1 continued

miRNAs	Injury model	Tissues	Times	Expression change	Functions	Refs
miR-133b	Spinal cord transection in zebrafish	Brainstem and spinal cord	7 d	Increased	Promoting axon growth	[84]
Peripheral nerve injury						
miR-21, miR-222	SNT in rats	Ipsilateral DRG	7 d	Increased	Inhibiting DRG neuron apoptosis	[87]
miR-21	SNT in rats and mice	Ipsilateral DRG	7 d	Increased	Promoting axon growth	[89]
miR-222	SNT in rats	Ipsilateral DRG	1, 4, and 7 d	Increased	Promoting axon growth	[90]
miR-138	SNT in mice	Ipsilateral DRG	7 d	Decreased	Inhibiting axon growth	[91]
miR-431	SNC in mice	Ipsilateral DRG	5 d	Increased	Promoting axon growth	[93]
miR-145	SNT in rats	Ipsilateral DRG	3 d	Decreased	Inhibiting axon growth	[94]
miR-182	SNT in rats	Sciatic nerve	0.5, 1, 3, 6, and 9 h	Increased	Inhibiting SC proliferation and migration	[102]
miR-221/222	SNT in rats	Sciatic nerve	1, 4, 7, and 14 d	Increased	Enhancing SC proliferation and migration	[103]
miR-9	SNT in rats	Sciatic nerve	1, 4, 7, and 14 d	Decreased	Inhibiting SC migration	[104]
Let-7	SNT in rats	Sciatic nerve	1, 4, 7, and 14 d	Increased and then decreased	Inhibiting SC proliferation and migration	[105]
miR-132	SNT in rats	Sciatic nerve	1, 4, 7, and 14 d	Increased	Enhancing SC migration	[106]
miR-34a, miR-140	SNC or SNT in mice	Sciatic nerve	4 and 14 d	Decreased and then increased	Inhibiting SC proliferation and remyelination respectively.	[110]
miR-29a	SNC	Sciatic nerve	4 or 5 d	Increased	Inhibiting SC myelination	[111]

BCCAO bilateral common carotid artery occlusion, *CCI* controlled cortical impact, *DRG* dorsal root ganglion, *FPI* fluid percussion injury, *LPS* lipopolysaccharide, *MCAO* middle cerebral artery occlusion, *NMDA N*-methyl-D-aspartic acid, *OGD* oxygen-glucose deprivation, *ONC* optic nerve crush, *Refs* references, *SC* Schwann cell, *SCI* spinal cord contusion injury, *SNC* sciatic nerve crush, *SNT* sciatic nerve transection.

expression by siRNA both enhance neurite outgrowth of DRG neurons [116].

Conclusions

The tissue-specific expression and functional roles of ncRNAs in the nervous system under physiological conditions determine their putative involvement in the pathophysiological processes of neural injury, which include immune/inflammatory responses, glial scar formation, neuronal apoptosis, cell proliferation and migration, axonal regrowth, and target organ re-innervation. After different types of CNS and PNS injury, such as ABI, SCI, and peripheral nerve injury, diverse ncRNAs, mainly miRNAs and lncRNAs, are differentially expressed in the injured neural tissue, and play unique regulatory roles through binding to the 3′-untranslated regions of target mRNAs, leading to translation repression or degradation of the mRNAs. The critical regulation of neural injury and regeneration is reflected in the promoting or suppressing effect on neuronal survival, neurite outgrowth, and glial phenotype.

The involvement of ncRNAs in numerous cellular processes and human diseases predicts that the two types of ncRNAs, miRNAs and lncRNAs, may be used as potential diagnostic biomarkers and therapeutic targets in the clinic. More importantly, both miRNAs and lncRNAs are readily detectable in bodily fluids, thus enabling them to be useful for therapeutic applications, including for neural injury [117]. However, neural injury is a complex process integrating multiple signaling pathways in the nervous, immune, and vascular systems, accompanied by various cellular and molecular mechanisms. Hence, single-target therapies are usually inadequate for treating neural injury. The further identification of ncRNAs whose expression is likely to be changed after neural injury will contribute to a global understanding of the molecular regulation of injury responses and regeneration, and will also facilitate the development of clinical applications of ncRNAs.

Another challenge to the potential use of ncRNAs in the clinic is the preparation of ncRNA amplifiers and inhibitors

and improving the relevant performance, including delivery, bioavailability, function, and adverse side-effects of both amplifiers and inhibitors. Currently, several preclinical animal studies have been reported. For example, implantation of a silicone tube injected with a 1:1 mixture of Matrigel and steroid-conjugated miR-9 agomir for bridging the rat sciatic nerve gap reduces Schwann cell migration within the tube due to increased expression of miR-9 [104]. Another example is that a silicone tube injected with a 1:1 mixture of Matrigel and let-7d antagomir enhances Schwann cell migration and axon outgrowth after implantation of the tube [105].

Importantly, a systems-level analysis of transcriptional changes in neural injury has been attracting increasing attention in that this new methodology can advance our understanding of ncRNA regulation. To conduct a systems-level analysis, massive data sets have been processed using Ingenuity Pathway Analysis [118], a web-based functional analysis tool, to generate gene networks, which may be used to search the signaling pathways and provide profound insights into the regulation of neural injury responses and regeneration at the transcriptional and post-transcriptional levels. Overall, further studies are needed to fully understand the functional roles of ncRNAs in neural injury and to actively develop ncRNA-based therapies for improving neural regeneration.

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