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The roles of microRNAs in spinal cord ischemia-reperfusion injury

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From the Contents

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Abstract

Spinal cord ischemia/reperfusion injury is a devastating medical disorder with poor prognosis that is associated with several pathophysiological conditions. However, multiple stimuli can trigger SCII, so the underlying mechanism of this pathology has not yet been fully established. MicroRNAs (miRNAs) are a class of non-coding RNAs that mediate a variety of nervous system diseases and regulate numerous physiological functions, including apoptosis, autophagy, inflammation, and blood-spinal cord barrier damage. miRNA expression profiles are known to be altered after spinal cord ischemia/reperfusion injury. Therefore, gaining a better understanding of the significant roles that miRNAs play in spinal cord ischemia/reperfusion injury could help develop potential preventive and therapeutic strategies for spinal cord ischemia/reperfusion injury. This review summarizes the current state of our knowledge about the relationship between miRNAs and spinal cord ischemia/reperfusion injury, as well as potential miRNAs that could be targeted to treat spinal cord ischemia/reperfusion injury.

Key Words: apoptosis; autophagy; blood-spinal cord barrier; inflammation; microRNAs; pathophysiology; review; spinal cord ischemia-reperfusion injury

Introduction

Spinal cord ischemia/reperfusion injury (SCII) is associated with many pathophysiological conditions such as intraspinal surgery, degenerative cervical myelopathy, and thoracoabdominal or thoracic aneurysm repair surgery (LeMaire et al., 2012; Karadimas et al., 2015; Chen et al., 2020b; Laliberte et al., 2021). Approximately 4–16% of patients with SCII patients have undergone thoracoabdominal aortic surgery (Zvara, 2002). Although numerous studies of potential SCII treatments have been performed, the neuroprotective effects of these interventions were limited, and SCII-associated neurological damage therefore remains a serious problem (Kahn et al., 2007; LeMaire et al., 2012). The etiology of SCII, which is caused by the induction of primary and secondary injury, is multifactorial. Many pathological processes, including inflammatory reactions, apoptosis, autophagy, blood-spinal cord barrier (BSCB) disruption, oxidative stress, mitophagy, and microglia activation play significant roles in the development of SCII (Li et al., 2017; Liu et al., 2017, 2018b; Zhao et al., 2018c; Ha Sen Ta et al., 2019).

Non-coding RNAs are RNAs that are not translated into proteins. They comprise transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), and small nuclear RNAs (snRNAs), as well as regulatory ncRNAs including PIWI-interacting RNAs (piRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs), and possibly other unknown types (Chandran et al., 2017). Non-coding RNAs regulate protein expression by influencing histone modification or DNA methylation, or by altering mRNA function (Liu et al., 2020a). In addition, non-coding RNAs such as circRNAs, lncRNAs and miRNAs are expressed in a developmental stage-specific manner during nervous system development and differentiation and regulate important aspects of central nervous system (CNS) function and development, including proliferation of neural progenitor cells and axon regeneration (Diaz et al., 2014; Ziats and Rennert, 2014; Wang et al., 2020a; Li et al., 2021). miRNAs regulate astrocyte and oligodendrocyte development, including cell proliferation, maturation, and myelin formation (Zheng et al., 2012). In addition, miRNAs are essential for the differentiation and morphological maturation of astrocytes in developing spinal cord white matter fibers (Li et al., 2016b).

miRNAs are highly conserved and composed of 20 to 24 nucleotides. miRNAs bind to the 3′-untranslated region (UTR) of target mRNAs to regulate posttranscriptional gene expression (Nieto-Diaz et al., 2014; Shi et al., 2017). Several steps are required to generate mature miRNAs from genomic DNA (Shi et al., 2017). Genomic DNA is transcribed into pri-miRNAs, which contain functional stem-loop hairpins, by RNA polymerase III or II (Saugstad, 2010). The Drosha-DGCR8 complex recognizes and cleaves the stem-loop structures to liberate a precursor microRNA (pre-miRNA). The pre-miRNA is exported from the nucleus to the cytosol, where it is processed by Dicer RNase III endonuclease to form a mature miRNA of approximately 22 to 25 nucleotides (Vasudeva and Munshi, 2020). Then, pri-miRNAs and pre-miRNAs are processed again by Dicer (dsRNA), and finally a single strand (mature miRNA) is incorporated into the RISC complex, forming miRISC (Akgül et al., 2022). The mature miRNAs bind to the 3′-UTRs of target mRNAs to negatively regulate gene expression at the posttranscriptional level (**Figure 1**) (Pan et al., 2017; Vasudeva and Munshi, 2020). miRNAs are estimated to regulate more than half of all genes in the human genome (Pinchi et al., 2019). A single mRNA may be regulated by multiple miRNAs, an individual miRNA can target many mRNAs, and different miRNAs can target the same genes with a synergic effect (Chandran et al., 2017; Shi et al., 2017). Therefore, multiple and complex regulatory networks can be formed between miRNA and downstream target genes.

Recent studies have shown that SCII can induce changes in miRNA expression, and that miRNAs act key regulatory roles in SCII (Hu et al., 2013; Liu et al., 2018b; Zhou et al., 2020). Therefore, a comprehensive understanding of the significant roles that miRNAs play in SCII could help develop preventive and therapeutic strategies for SCII. This review aims to summarize our current knowledge regarding the regulatory roles of miRNAs in the pathophysiology of SCII.

Search Strategy

The PubMed database was searched up to December 2020 for studies regarding the roles of miRNAs in SCII. The following terms were used to search for relevant studies: “spinal cord” or “ischemia or hypoxia” in combination with “microRNA or miRNA”.

Studies were included based on the following criteria: (1) the study was related to the roles of miRNAs following SCII; (2) the study was an Original Study. In total, 68 studies were retrieved using the search terms described above. Studies were excluded if they met the following criteria: (1) non-English articles; (2) one of the following article types: letters, review articles, meta-analyses, and abstracts. The retrieved articles were checked by two investigators, and relevant information was extracted from each included article (An et al., 2014). Only those studies related to the roles of miRNAs following SCII were ultimately included.

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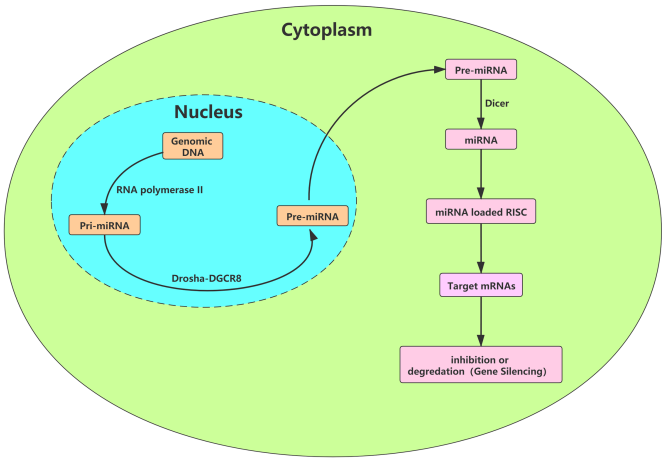

Figure 1 | **miRNA biogenesis and function.**
Genomic DNA is transcribed into pri-miRNAs, which contain functional stem-loop hairpins, by RNA polymerase III or II. The Drosha-DGCR8 complex recognizes and cleaves the stem-loop structures to liberate a precursor microRNA (pre-miRNA). The pre-miRNA is exported from the nucleus to the cytosol, where it is processed by Dicer RNase III endonuclease to form a mature miRNA. Then, pri-miRNAs and pre-miRNAs are processed again by Dicer (dsRNA), and finally a single strand (mature miRNA) is incorporated into the RISC complex, forming miRISC. The mature miRNAs bind to the 3′-UTRs of target mRNAs to negatively regulate gene expression at the posttranscriptional level.

MicroRNAs in Normal and Pathological Central Nervous System States

Numerous studies have demonstrated that miRNAs are abundant in the CNS (Pan et al., 2017; Pinchi et al., 2019; Vasudeva and Munshi, 2020; Wang et al., 2021a, b). miRNAs play important roles in CNS development, neuronal differentiation, and synapsis shaping and are closely linked to CNS function (Kozuka et al., 2019; Shu et al., 2019; Glaesel et al., 2020). During brain development, miRNAs show specific and dynamic spatial and temporal patterns of expression, and 75 miRNAs have been shown to be differentially expressed throughout development within different brain regions (Ziats and Rennert, 2014). A recent study showed that multiple miRNAs display spatially enriched/restricted expression patterns in specific neuron subtypes or in anatomically distinct regions in the embryonic spinal cord and brain. For example, miR-23a and miR-218 are expressed in motor neurons located in the ventrolateral spinal cord, and miR-137 is enriched in the cerebral peduncle of the midbrain dorsolateral nucleus, the ventral posterolateral nucleus of the thalamus, the nucleus accumbens and striatum of the telencephalon, and the dorsolateral nucleus and ventral posterolateral nucleus of the thalamus (Shu et al., 2019). In addition to detecting miRNA expression patterns, many studies have also explored the various functions of specific miRNAs during neural development and brain activities (Davis et al., 2015). For example, proliferation of neural progenitor cells in human embryonic stem cells is promoted by overexpression of miR-9 (Delaloy et al., 2010). miR-124 regulates the transcriptional repressor REST in neuronal differentiation, whereby REST represses expression of neuronal genes and miR-124a in neural progenitor and nonneuronal cells (Conaco et al., 2006). Many miRNAs are known to be involved in neurological disorders, such as SCII, stroke, Parkinson's disease (PD), Alzheimer's disease (AD), spinal cord injury (SCI), traumatic brain injury (TBI), multiple sclerosis (MS), and vascular cognitive impairment and dementia (Liu et al., 2009; Strickland et al., 2011; Chen et al., 2020a; Ma et al., 2020; Sun et al., 2020; Xiao et al., 2020; Gao et al., 2021; Lin et al., 2021; Zeng et al., 2021). miRNAs are considered to be critical regulators of multiple biological processes involved in neurological disorders, such as inflammation and oxidative stress, apoptosis, neurogenesis, cellular differentiation, and maintenance during physiological and pathological processes (Chandran et al., 2017; Yan et al., 2019). It has been shown that miRNAs are potential new targets for the prevention and treatment of SCII, and their regulation of target genes may play important roles in SCII (Chen et al., 2020a).

The roles of miRNAs in normal and pathological CNS states are displayed in **Figure 2**.

Pathophysiology of Spinal Cord Ischemia/Reperfusion Injury

The etiology of SCII, which is caused by the induction of primary and secondary injury, is multifactorial. Many pathological processes, including inflammatory reactions, apoptosis, autophagy, BSCB disruption, oxidative stress, intracellular calcium overload, and excitatory amino acid toxicity, play key roles in the development of SCII (**Figure 3**) (Li et al., 2017; Liu et al., 2017, 2018b; Zhao et al., 2018c; Ha Sen Ta et al., 2019).

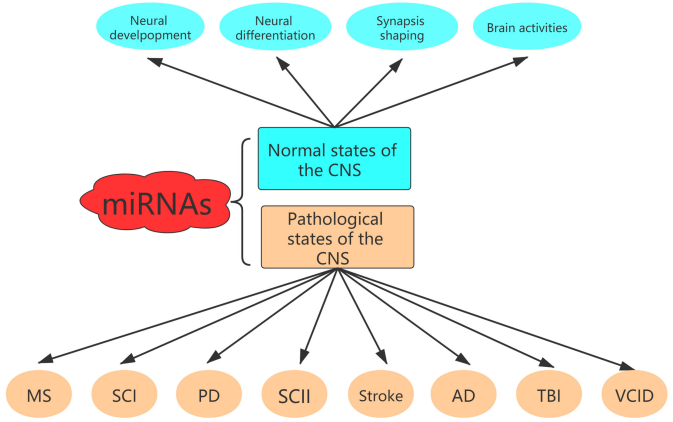

Figure 2 | **miRNAs in normal and pathological central nervous system states.**
miRNAs are involved in neurological disorders, such as SCII, stroke, PD, AD, SCI, TBI, MS, and VCID. AD: Alzheimer's disease; CNS: central nervous system; miRNA: microRNAs; MS: multiple sclerosis; PD: Parkinson's disease; SCI: spinal cord injury; SCII: spinal cord ischemia-reperfusion injury; TBI: traumatic brain injury; VCID: vascular cognitive impairment and dementia.

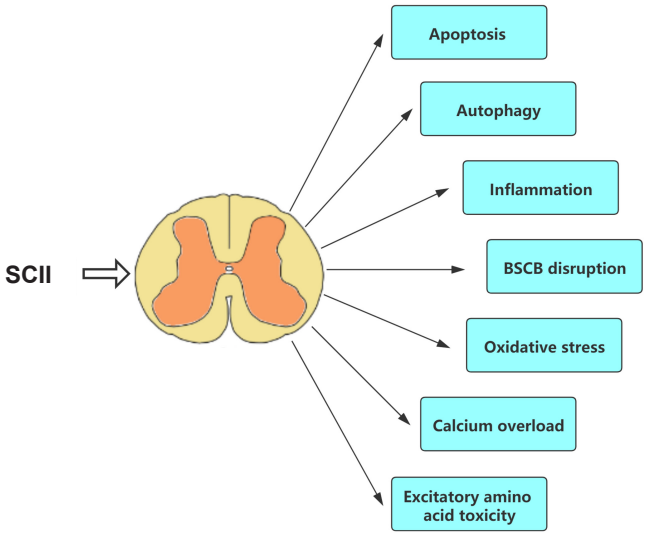

Figure 3 | **Pathophysiology of SCII.**
Many pathological processes, including inflammatory reactions, apoptosis, autophagy, blood-spinal cord barrier disruption, oxidative stress, intracellular calcium overload, and excitatory amino acid toxicity, play key roles in the development of SCII. BSCB: Blood-spinal cord barrier; SCII: spinal cord ischemia-reperfusion injury.

Apoptosis and autophagy

Apoptosis is an important mechanism that occurs in response to cell damage and can aggravate spinal cord injury after SCII (Yang et al., 2012). The apoptotic cells in this context are mainly nerve cells, which leads to limb paralysis following SCII (Fan et al., 2011). Caspase-related apoptotic mechanisms contribute to SCII-induced neural cell apoptosis (Zhao et al., 2018b). In addition, altered levels of the pro-apoptotic proteins p53 and Bax and the anti-apoptotic protein Bcl-2 have been closely linked to SCII (Zhu et al., 2015; Li et al., 2018c). Autophagy, of which there are three types (macroautophagy, microautophagy, and chaperone-mediated autophagy), is an evolutionarily conserved self-degradation process involving the decomposition and circulation of organelles, lipids, and long-lived proteins, and is crucial for cell homeostasis and survival (Huang et al., 2019). Early activation of autophagy alleviates SCII by inhibiting inflammation and apoptosis; however, at later timepoints, excessively elevated autophagy induces autophagic cell death, which worsens SCII (Fang et al., 2016).

Inflammation

An inflammatory response follows short-term and long-term spinal cord ischemia and the main cause of delayed neuronal death (Papakostas et al., 2006). Microglia, lymphocytes, macrophages, astrocytes, and neutrophils participate in SCII as inflammatory cells (Zhu et al., 2013). Cytokines and chemokines such as chemokine (C-X-C motif) ligand 13 (CXCL13), interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α (TNF-α), and IL-10 are important mediators of the inflammatory response in spinal cord tissues following SCII and contribute to spinal cord injury (Chen et al., 2020b).

BSCB disruption

BSCB has important physiological significance in maintaining the relative

stability of the internal environment of the nervous system. Maintaining the integrity of the BSCB alleviates spinal cord injury after spinal cord ischemia (Hu et al., 2016). Following SCII, the permeability of the BSCB increases; the tight junction proteins claudin-5, occludin, and ZO-1 in the barrier are destroyed; the microvessels are destroyed; and apoptosis of pericytes and endothelial cells increases, indicating that the BSCB has been disrupted, allowing inflammatory cells to infiltrate into spinal cord tissue and aggravate spinal cord damage (Zhu et al., 2013; Hu et al., 2016). Matrix metalloproteinases (MMPs) directly increase BSCB permeability (Li et al., 2014b). Excessive MMP proteolytic activity can lead to the destruction of the BSCB after SCII; inhibition of MMP activity can prevent BSCB destruction, reduce cell death, weaken the inflammatory response, and improve functional recovery (Zhang et al., 2021).

Oxidative stress

Excessive production of reactive oxygen free radicals damages normal human cells and tissues. Spinal cord ischemia induces the production of a large number of reactive oxygen free radicals, as well as lipid peroxidation, which aggravates tissue edema and increases vascular permeability (Qu et al., 2009). During ischemia/reperfusion (I/R) injury, oxygen free radicals are produced, which activate several enzymes, including phospholipase A, and causes further damage to the biological lipid membrane (Chen et al., 2011). The integrity and permeability of cell membranes in the nervous system is destroyed by free radicals, resulting in cell death and reperfusion injury (Hall et al., 2016).

Calcium overload

Maintaining a stable intracellular Ca^{2+} concentration is the basis for various normal physiological functions (Xue et al., 2017). Various mechanisms can lead to Ca^{2+} influx into nerve cells, resulting in Ca^{2+} overload, which is considered to be the last possible pathway for nerve cell death following SCII (Jalc et al., 1995). Intracellular Ca^{2+} overload activates Ca^{2+}-dependent calpain activity, which leads to degradation of a variety of cytoskeletal proteins, vesicular changes in myelin proteins, axonal degeneration, destruction of cell structure, and finally nerve cell death (Bano and Ankarcrona, 2018).

Excitatory amino acid toxicity

As an excitatory amino acid (EAA), glutamate is present at high concentrations in a number of disorders of the CNS (Palmada and Centelles, 1998). The excessive extracellular concentrations of EAAs induced by ischemic injury in the CNS may be toxic to neurons (Kimura et al., 2021). There is a strong positive correlation between increased EAA concentrations and spinal cord ischemia caused by aortic cross-clamp (Ishikawa and Marsala, 1999). Excessive extracellular EAAs activate their receptors (mainly the NMDA receptor), which induces a lethal influx of excessive calcium, resulting in neuronal injury (excitotoxicity) (Arundine and Tymianski, 2003).

MicroRNAs in Spinal Cord Ischemia/Reperfusion Injury

miRNA expression profiles in spinal cord tissues of animal models

Altered miRNA expression in spinal cord tissues in a rat model of SCII was reported in 2013 (Hu et al., 2013). The authors demonstrated alterations in miRNA expression levels in the spinal cord 48 hours after reperfusion using a microarray platform. They found that 10 miRNAs were downregulated, whereas 38 miRNAs were up-regulated. Potential target mRNAs of the altered miRNAs were identified by searching the TargetScan database to determine the pathophysiological relevance of altered miRNA expression after SCII. The analysis indicated that the potential targets for these miRNAs are involved in a number of pathophysiological processes such as inflammation, neuronal damage, and apoptosis following SCII (Hu et al., 2013). This study illustrated that miRNAs participate in SCII by regulating corresponding target genes.

Another study demonstrated that miR-22-3p was continuously upregulated in a rat model of spinal cord ischemia in response to three different reperfusion conditions (90-minute ischemia; ischemia + 24-hour reperfusion; and ischemia + 48-hour reperfusion), whereas miR-144-5p, miR-743b-3p, and miR-201-5p were downregulated in all three cases (Li et al., 2016a). In addition, Tmem69 and Cxcl10 were negatively regulated by all four miRNAs.

A recent study detected miRNA expression profiles at 24 and 48 hours following SCII induced by abdominal aorta occlusion for 90 minutes (Liu et al., 2020b). The study demonstrated that, at 24 hours after SCII, 13 miRNAs were aberrantly expressed, including one downregulated miRNA and 12 upregulated miRNAs. At 48 hours after SCII, 105 miRNAs were differentially expressed, including 61 downregulated miRNAs and 44 upregulated miRNAs. Among the aberrantly expressed miRNAs, only miR-22-3p was upregulated at both timepoints that were assessed after SCII.

The miRNA expression profiles in the spinal cord tissues of animal models reported in the three studies described above are shown in **Figure 4**.

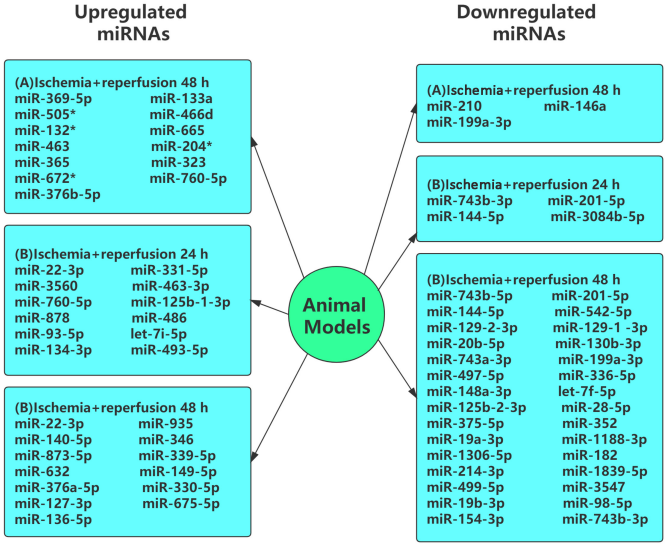

Figure 4 | **miRNA expression profiles in spinal cord tissues of animal models.**
(A) Spinal cord ischemia-reperfusion injury was induced by ligation of abdominal aorta just below the left renal artery for 60 minutes. (B) Spinal cord ischemia-reperfusion injury was induced by abdominal aorta occlusion for 90 minutes.

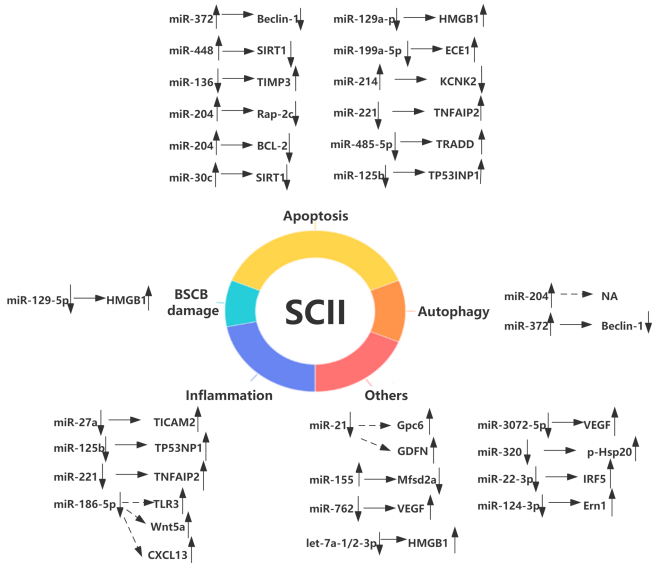

Figure 5 | **miRNAs in the pathophysiology of SCII.**
miRNAs trigger or inhibit a series of pathophysiological responses in SCII, including inflammation, apoptosis, autophagy, BSCB damage, and more. Moreover, some specific miRNAs simultaneously regulate various mechanisms to regulate SCII pathophysiology. "↑" indicates upregulation following SCII, and "↓" indicates downregulation following SCII. Target genes are also shown (indirect or predicted target genes are indicated with a dashed arrow, whereas those with confirmed regulation are shown with a solid arrow). BCL-2: B-cell lymphoma 2; BSCB: blood-spinal cord barrier; CXCL13: chemokine (C-X-C motif) ligand 13; ECE1: endothelin-converting enzyme-1; Ern1: endoplasmic reticulum to nucleus signaling 1; GDFN: glial cell line–derived neurotrophic factor; Gpc6: glypican; HMGB1: high mobility group box 1; IRF5: interferon regulatory factor 5; KCNK2: mammalian K2P2.1 potassium channel; Mfsd2a: Major facilitator superfamily domain containing 2a; NA: not available; p-Hsp20: phosphorylation state of heat-shock protein 20; Rap-2c: ras-related protein Rap-2c; SCII: spinal cord ischemia-reperfusion injury; SIRT1: Sirtuin 1; SP1: specificity protein 1; TICAM-2: toll-like receptor adaptor molecule 1; TIMP3: tissue inhibitor of metalloproteinases-3; TLR3: Toll-like receptor 3; TP53INP1: tumor protein 53-induced nuclear protein 1; TNFAIP2: TNF-α induced protein 2; TRADD: tumor necrosis factor receptor type 1-associated DEATH domain protein; VEGF: vascular endothelial growth factor.

Regulatory Roles of MicroRNAs in Spinal Cord Ischemia/Reperfusion Injury

The regulatory roles that miRNAs play in SCII are complex and overlapping (**Figure 5**) (Hu et al., 2013; Wang et al., 2016, 2021a). A single miRNA might regulate a variety of biological processes in SCII (Ma et al., 2017; Wang et al., 2018a; Zhao et al., 2018a). In the context of SCII, miRNAs mainly regulating apoptosis, autophagy, inflammation, and BSCB disruption (Li et al., 2015b; Yan et al., 2019). **Table 1** presents a summary of the miRNAs, target genes, upregulation or downregulation, timepoints post-SCII, injury models, and biological functions that will be discussed below.

Regulation of apoptosis

Apoptosis is a well-recognized mechanism of neuronal death induced by I/R injury (Li et al., 2018a). Many miRNAs are involved in SCII pathogenesis, such as miR-204 (Qiao et al., 2017), miR-199a-5p (Bao et al., 2018), miR-448 (Wang et al., 2018b), miR-129-5p (Li et al., 2017), miR-136 (Jin et al., 2017), and

Table 1 | **Roles of different miRNAs in SCII**

ID	Models	Expression	Time points after reperfusion	Target genes	Biological function	Study
miR-204	Male Wistar rats (250 g)	Upregulated	6, 12, 24 h	NA	miR-204 shows protective effects possibly via promotion of autophagy and antiapoptotic effects.	Yan et al., 2019
	Adult male C57/BL6 mice	Upregulated	NA	Rap-2c	miR-204 inhibitor decreases the apoptosis rate.	Qiao et al., 2017
	PC12 and AGE1.HN cells					
	SD rats (12 weeks old, 220–300 g)	Upregulated	NA	NA	Knockdown of miR-204 reduces cell apoptosis.	Qiao et al., 2018
	Patients compared with healthy control	Upregulated	NA	NA	NA	Wang et al., 2016
	AGE1.HN and PC12 cells	Upregulated	6, 12, 24 h	BCL-2	HIF-1α-miR-204-BCL-2 axis induces apoptosis of neuronal cells caused by hypoxia.	
miR-199a-5p	Male SD rats (220–280 g)	Downregulated	24 h	ECE1	Upregulation miR-199a-5p might alleviate SCII-induced apoptosis.	Bao et al., 2018
miR-448	Adult male SD rats (250–320 g)	Upregulated	NA	SIRT1	Downregulated miR-448 reduces apoptosis of nerve cells and improved neurological function.	Wang et al., 2018
	PC12 and AGE1.HN cells					
miR-372	Adult male SD rats (200–220 g)	Upregulated	48 h	Beclin-1	Knockdown of miR-372 reduces nerve cell apoptosis in SCII via increasing autophagy.	Li et al., 2018a
	PC12 cells	Upregulated	NA			
miR-21	Male Wistar rats (250 g)	NA	2 h	Faslg, PDCD4	Overexpression of miRNA-21 shows anti-apoptosis effects.	He et al., 2016
miR-136	Adult male SD rats	Downregulated	20 d	TIMP3	miR-136 overexpression reduced cell apoptosis that caused by SCII.	Jin et al., 2017
	PC12 and AGE1.HN cells	Downregulated	NA			
miR-214	Male SD rats (8 weeks old)	Upregulated	NA	KCNK2	miR-214-dependent KCNK2 inhibition contributed to the exacerbation of apoptosis.	Liu et al., 2020
	PC12 cells					
miR-485-5p	Clinical and radiologic signs of cervical spondylotic myelopathy patients and healthy controls	Downregulated (serum)*	NA	NA	NA	Chen et al., 2016
	SY-SH-5Y and AGE1.HN cells	Downregulated	NA	TRADD	miR-485-5p-mediated targeting of TRADD signaling might be involved in apoptosis reducing effects of hydrogen sulfide.	
miR-186-5p	Male SD rats (200–250 g)	Downregulated	12, 24, 36 h	TLR3, Wnt5a, CXCL13	Mimic-186-5p reduces neuroinflammation.	Chen et al., 2020
miR-27a	Male SD rats (200–250 g)	Downregulated	24, 72 h	TICAM-2	miR-27a upregulation attenuates neuroinflammation.	Li et al., 2015b
miR-128-3p	Male SD rats (200–250 g)	Downregulated	6, 12, 24, 36, 48 h	SP1	miR-128-3p reduces neuroinflammation and apoptosis in SCII partially by downregulating SP1.	Wang et al., 2020a
miR-125b	SD rats (8 weeks old, 200–250 g)	Downregulated	12, 24, 36, 48 h	TP53INP1	miR-125b mimic protectes neurons against aberrant p53 network activation-induced apoptosis and neuroinflammation	Li et al., 2018b
miR-221	Patients and healthy controls	Downregulated (serum)*	NA	NA	NA	Zhao et al., 2018
	SY-SH-5Y and AGE1.HN cells	Downregulated	NA	TNFAIP2	miR-221 overexpression reduces cell apoptosis of neuronal cell and the inflammatory response.	
miR-21	Neurotrophic reactive astrocytes(A2s)	Downregulated	NA	Gpc6, GDFN	Silencing miR-21 induces the formation of synapses and improves polarization of astrocytes to the A2 phenotype.	Su et al., 2019
miR-124	Male Wistar rats (250 g)	NS	NA	iASPP	Inhibition of miR-124 shows neuroprotection possibly by induction of antiapoptotic and mitophagy effects.	Liu et al., 2017
miR-30c	Male SD rats (300–350 g)	NA	NA	Beclin-1	Hydrogen sulfide(H2S) protects spinal cord and induces autophagy via miR-30c.	Li et al., 2015a
	SY-SH-5Y cells					
	Rats	Upregulated	NA	Beclin-1	Inhibition of miR-30c in OGD/R-induced SY-SH-5Y cell with H_2S preconditioning reduces cell apoptosis.	Liu et al., 2018
	SY-SH-5Y cells					
	Male SD rats (250–300 g)	Upregulated	12, 24, 48 h	SIRT1	Abrogation of miR-30c inhibits SCII through targeting SIRT1.	Wang et al., 2019
	PC12 cells	Upregulated	NA			
miR-129-5p	C57BL6 mice (12–15 weeks old)	Downregulated	12, 24, 36, 48 h	HMGB1	Increasing miR-129-5p ameliorates inflammation-induced neuronal and BCSB damage.	Li et al., 2017
miR-320	Male Wistar rats (230–270 g)	Downregulated	6 h	phospho-Hsp20	Inhibition of miR-320 increases the number of intact motor neurons in the lumbar spinal cord and improves neurological function.	He et al., 2015
miR-125a-5p	Rat spinal cord microvascular endothelial cells (SCMECs) and astrocytes	NA	NA	ZO-1, occludin, VE-cadherin	miR-125a-5p reduces the permeability of the BSCB by increasing the expression of ZO-1, occludin, and VE-cadherin and their mRNA, and against hypoxia-induced apoptosis of spinal cord microvascular endothelial cells.	Wang et al., 2020b
miR-155	C57Bl/6 mice and miR-155 global knockout (miR-155$^{-/-}$) mice in C57Bl/6 background (10–12 weeks old, 20–22 g)	Upregulated	48 h	Mfsd2a	miR-155 ablation slows the progression of central cord edema and reduces the incidence of paralysis by 40%.	Awad et al., 2018
Let-7a-1/2-3p	Male C57BL/6 mice (10–12 weeks old)	Downregulated	60 h	HMGB1	Dexmedetomidine inhibits the activation of microglial cell by upregulates Let-7a-1/2-3p expression.	Ha Sen Ta et al., 2019
	Microglia	Downregulated	NA			
miR-25	Adult male SD rats (250 g)	NS	NA	NA	miR-25-enriched exosomes enhances miR-25 level, reduces NADPH oxidase 4 expression, decreases malondialdehyde content, and increases superoxide dismutase activity.	Zhao et al., 2019
miR-762 miR-3072-5p	Male C57BL/6 mice	Downregulated	24 h (exosomal microRNAs in plasma)	VEGF	Ischemic preconditioning increases plasma VEGF levels and is associated with downregulation of miR-3072-5p and miR-762.	Ueno et al., 2016
miR-22-3p	Male SD rats (3–4 months old, 250–260 g)	Downregulated	12, 24, 36, 48 h	IRF5	Overexpression of miR-22-3p inhibits protects SCII by repressing IRF5 in macrophages.	Fang et al., 2021
	Macrophages		NA			
miR-124-3p	Males SD rats (8 weeks old)	Downregulated	6 h	Ern1	Exosomal miR-124-3p derived from bone marrow mesenchymal stem cells reduces SCII by M2 macrophage polarization and regulating Ern1.	Li et al., 2020
	Macrophages		NA			

miRNAs can be used as therapeutic targets in SCII. The table lists regulation of miRNAs in different animal models and the target gene or predicted target gene. * indicates that samples were obtained from serum, while other samples were obtained from spinal cord tissues or cells. BCL-2: B-cell lymphoma 2; BSCB: blood-spinal cord barrier; CXCL13: chemokine (C-X-C motif) ligand 13; ECE1: endothelin-converting enzyme-1; Ern1: endoplasmic reticulum to nucleus signaling 1; Faslg: Fas ligand; GDFN: glial cell line-derived neurotrophic factor; Gpc6: glypican; HIF-1α: hypoxia-inducible factor-1α; HMGB1: high mobility group box 1; iASPP: inhibitory member of the apoptosis stimulating proteins of p53 family; IRF5: interferon regulatory factor 5; KCNK2: mammalian K2P2.1 potassium channel; Mfsd2a: major facilitator superfamily domain containing 2a; NA: not available; NADPH: nicotinamide adenine dinucleotide-phosphate; NS: not significant; OGD/R: oxygen-glucose deprivation and reperfusion; PDCD4: programmed cell death 4; phospho-Hsp20: phosphorylation state of heat-shock protein 20; Rap2c: Ras-related protein Rap2c; SD: Sprague-Dawley; SIRT1: Sirtuin 1; SP1: specificity protein 1; TICAM-2: toll-like receptor adaptor molecule 1; TIMP3: tissue inhibitor of metalloproteinases-3; TLR3: Toll-like receptor 3; TNFAIP2: TNF-α induced protein 2; TP53INP1: tumor protein 53-induced nuclear protein 1; TRADD: tumor necrosis factor receptor type 1-associated DEATH domain protein; VE-cadherin: vascular endothelial-cadherin; VEGF: vascular endothelial growth factor; ZO-1: zonula occluden-1.

miR-485-5p (Chen et al., 2016). miR-204 has been studied in CNS disorders (Xiang et al., 2016; Wang et al., 2018c). A previous study demonstrated hypoxia-induced miR-204 expression in neuronal cells (Wang et al., 2016). Transfection with miR-204 inhibitors significantly decreased neuronal proliferation and significantly increased neuronal apoptosis in hypoxic-ischemic encephalopathy (Chen et al., 2019). It has also been reported that the HIF-1a-miR-204-BCL-2 pathway induces apoptosis in SCII (Wang et al., 2016). Inhibition of miR-204 results in autophagy and antiapoptotic effects, which protect against SCII (Yan et al., 2019). Another study has also shown that MALAT1 exerts antiapoptotic effects in a rat model of SCII by regulating miR-204 (Qiao et al., 2018). As a newly discovered member of the Ras-related protein (Rap) 2 subfamily of proteins, Rap2c binds guanine nucleotides with specific properties and acts on Rap2-mediated signal transduction to regulate neuronal structure (Qiao et al., 2017). Inhibition of miR-204 decreases the rate of cell apoptosis via upregulation of Rap2c expression following SCII (Qiao et al., 2017). miR-199a-5p is expressed in the brain and spinal cord (Feng et al., 2017; Bao et al., 2018). Inhibition of miR-199a-5p reduces SCII-induced neuronal cell damage through the CAV-1–mediated MEK/ERK pathway (Zhong et al., 2020). Inhibition of miR-199a-5p protects against OGD/R-induced oxidative stress and apoptosis (Rong et al., 2020). The gene encoding endothelin-converting enzyme 1 may be a novel hypoxia-inducible factor target gene, as demonstrated both *in vivo* and *in vitro* (Khamaisi et al., 2015). ECE-1 is involved in the development of subarachnoid hemorrhage and AD (Wang et al., 2010; Kuruppu et al., 2014). miR-199a-5p reduces endothelin-converting enzyme 1 to alleviate SCII-induced apoptosis (Bao et al., 2018). This difference in miR-199a-5p function may be due to differences in the diseases, models, or timepoints. miR-448 levels were greatly increased in rat hippocampus following chronic lead exposure, which suggests that this miRNA may be associated with neurodegenerative disease and neurophysiological pathways (Kong et al., 2014). It has been reported that sirtuin-1 (SIRT1) plays a significant role in oxidative stress, apoptosis, and inflammation under ischemic/hypoxic conditions (Meng et al., 2017). Downregulation of miR-448 is reported to improve neurological function and mitigate nerve cell apoptosis by upregulating SIRT1 in SCII (Wang et al., 2018b). Studies have shown that miR-129-5p is associated with CNS disease (Zhou et al., 2018). We explored the role of miR-129-5p after SCII and found that its expression decreased with time (12, 24, 36, and 48 hours) (Li et al., 2017). HMGB1 levels in the spinal cord and serum increased significantly in a rabbit model of SCII, which was related to the protective effects of hydrogen gas against SCII (Huang et al., 2011). miR-129-5p inhibits HMGB1 and TLR3-associated cytokines to alleviate SCII-induced neuronal damage (Li et al., 2017). miR-136 acts as a vital biomarker and plays a key role in different diseases, including cerebral I/R injury (Zhong et al., 2019). miR-136 has also been widely studied in CNS disease. As a member of the tissue inhibitor of metalloproteinase (TIMP) family, TIMP3 has demonstrated a broad range of metalloproteinase inhibitory activity against MMP family members (Su et al., 2019a). miR-136 overexpression reduces cell apoptosis following SCII by targeting TIMP3 (Jin et al., 2017). miR-485-5p-mediated targeting of tumor necrosis factor receptor type 1-associated DEATH domain protein (TRADD) signaling may be involved in apoptosis by reducing the effects of hydrogen sulfide in SCII (Chen et al., 2016). In addition, miR-372 (Zhao et al., 2018c), miR-124 (Liu et al., 2017), miR-221 (Zhao et al., 2018a), miR-125b (Li et al., 2018c), miR-21 (He et al., 2016), miR-30c (Zhou et al., 2018), and miR-214 (Chen et al., 2020a) could also regulate apoptosis in the context of SCII. Taken together, these studies suggest that apoptosis in SCII is regulated by miRNAs.

Regulation of autophagy

Studies have demonstrated that miRNAs regulate autophagy in SCII (Li et al., 2015b; Liu et al., 2017, 2018b; Wang et al., 2019a; Yan et al., 2019). miR-372 is involved in autophagy (Chen et al., 2017). Beclin-1, which is the first mammalian autophagy protein identified, and was originally identified as a Bcl-2-interacting protein, plays an important role in autophagy (Xu and Qin, 2019). A previous study demonstrated that Beclin-1-overexpressing neuronal cells showed lower levels of apoptosis, greater cell viability, and enhanced LC3II/LC3I conversion following mechanical injury (Wang et al., 2014). Knockdown of miR-372 enhanced autophagy and upregulated Beclin-1, thereby protecting against SCII (Zhao et al., 2018c). miR-204 is also involved in autophagy (Wang et al., 2019a). The promotion of antiapoptotic effects and autophagy is involved in the protective effects of miR-204 downregulation (Yan et al., 2019). miR-124 is highly expressed in the embryonic and adult brain and plays a significant role in the transformation of neural stem cells into mature neurons (Cheng et al., 2009; Liu et al., 2017). It has been reported that inhibitory member of the apoptosis-stimulating proteins of the p53 family (iASPP) may be associated with neuronal death after stroke (Liu et al., 2018a). Downregulation of miR-124 induced iASPP expression and markedly reduced infarction in a mouse model of focal cerebral ischemia (Liu et al., 2013). Induction of mitophagy leads to the selective clearance of damaged mitochondria before activating cell death (Liu et al., 2017). Mitophagy is involved in the pathophysiology of hemorrhagic stroke and I/R injury (Liu et al., 2018b). Inhibition of miR-124 was shown to increase iASPP expression, which protected against SCII, possibly by induction of antiapoptotic effects and mitophagy (Liu et al., 2017). Hydrogen sulfide alleviated SCII by inducing autophagy via regulation of the miR-30c/Beclin1 axis (Li et al., 2015b; Liu et al., 2018b).

Regulation of neuroinflammation

It is well-accepted that the inflammatory response plays a key role in SCII (Gokce et al., 2016). Several miRNAs, including miR-27a, miR-125b, miR-221, and miR-186-5p, have been shown to be involved in the inflammatory response that occurs with SCII (Li et al., 2015b, 2018c; Zhao et al., 2018a; Chen et al., 2020a). miR-27a contributes to the regulation of multiple biological reactions, as well as the pathogenesis of various diseases (Cai et al., 2019). SCII causes TLR4 pathway activation and initiates neuroinflammation via the NF-κB/IL-1β pathway (Li et al., 2014a). miR-27a mimics inhibit the NF-κB/IL-1β pathway and TICAM-2 within the TLR4 signaling pathway to reduce SCII-induced inflammation (Li et al., 2015b). miR-125b plays a significant role in the abnormal development of the spinal cord (Zhao et al., 2008). miR-125b mimics reduce aberrant p53 network activation-induced neuroinflammation and apoptosis to protect against SCII (Li et al., 2018c). miR-221 regulates multiple physiological and pathological processes, especially in I/R injury and in the context of an inflammatory response (Corsten et al., 2015; Zhao et al., 2018a). miR-221 levels were decreased in blood samples from 20 patients with SCII compared with healthy controls (Zhao et al., 2018a). TNFα-induced protein 2 (TNFAIP2) is a major response gene induced by a variety of pro-inflammatory molecules at the transcriptional activation level (Jia et al., 2018). miR-221 overexpression partly alleviates the inflammatory response by targeting TNFAIP2 in SCII *in vivo* (Zhao et al., 2018a). Thus, these miRNAs are potential therapeutic targets for reducing neuroinflammation in SCII.

Regulation of BSCB disruption

Disruption of the BSCB is a main pathological change that can amplify inflammation, increase leukocyte infiltration, and exacerbate spinal cord edema (Yu et al., 2016). BSCB damage can be induced by the inflammatory reaction (Li et al., 2014a), oxidative stress (Lochhead et al., 2010), decreased MMP-9 expression (Fang et al., 2013; Li et al., 2014b), and dysregulation of aquaporin-4 (AQP4) (Zhang et al., 2015). miR-320 is differentially expressed in brain tissue following focal cerebral I/R injury (Liang et al., 2018). miR-320 regulates insulin-like growth factor 1 (IGF-1) to aggravate apoptosis within the ipsilateral cortical infarcted peripheral zone and increases edema volume and brain infarction volume via regulation of IGF-1 following cerebral I/R injury in mice (Liang et al., 2018). miR-27a mimics reduce neuroinflammation-induced BSCB damage following SCII (Li et al., 2015b). miR-125a-5p appears to reduce BSCB damage by upregulating the expression of ZO-1, occludin, and VE-cadherin (Wang et al., 2020b). Overexpression of miR-129-5p protects against SCII by decreasing inflammation-induced BCSB (Li et al., 2017). Targeting these miRNAs, which help maintain the integrity of the BSCB, could therefore help ameliorate SCII (Yang et al., 2016; Jing et al., 2020).

Regulation of other SCII pathological mechanisms

miRNAs also regulated other pathological mechanisms involved in SCII, such as astrocyte polarization (Su et al., 2019b), central cord edema (Awad et al., 2018), and microglial cell activation (Ha Sen Ta et al., 2019). Silencing miR-21 induces the formation of synapses and improves polarization of astrocytes to the A2 phenotype through the signal transducer and activator of transcription-3 (STAT3)-glial cell line-derived neurotrophic factor pathway and STAT3-glypican 6 pathway after SCII (Su et al., 2019b). miR-155 ablation has been shown to reduce the incidence of paralysis by 40% and slow the progression of central cord edema through the regulation of Mfsd2a in a mouse model of aortic aneurysm repair (Awad et al., 2018). Dexmedetomidine inhibits microglial cell activation by regulating Let-7a-1/2-3p expression in the spinal cord of SCII mice (Ha Sen Ta et al., 2019). miR-25–enriched exosomes significantly lower motor deficit index scores and increase neuronal survival by increasing superoxide dismutase activity, decreasing malondialdehyde content, and inhibiting NADPH oxidase 4 expression in spinal cord tissues in SCII (Liu et al., 2019). Remote ischemic preconditioning transiently increased plasma vascular endothelial growth factor (VEGF) levels by reducing miR-3072-5p and miR-762 in CD34-positive BM cells (Ueno et al., 2016).

Limitations

While the present review aimed to be comprehensive, it has a number of limitations. First, the fact that papers were only retrieved by searching PubMed means that it is likely that some relevant publications were missed, and while PubMed is a widely-used and influential database, it is possible that prominent articles were not included. Second, as the publication search only extended until December 2020, more recent research or papers in progress would not have been included. Finally, non-English papers were excluded from this review, even though they are included in PubMed.

Future Perspectives and Conclusion

Differential expression of miRNAs has been detected at different timepoints after SCII in the spinal cord tissue of rats. miRNAs bind to target mRNAs and prevent their expression at the post-transcriptional level. In addition, some miRNAs appear to be regulated by special lncRNAs in the context of SCII. There are challenges associated with the use of miRNAs as preventive and therapeutic interventions. The molecular mechanisms by which non-coding RNAs contribute to SCII remain largely elusive. Furthermore, miRNA interventions may affect healthy organs, as well as the injured spinal cord, as the spinal cord may not be the only target of these molecules. Therefore, the biology of miRNAs needs further exploration. More efficient miRNA delivery systems that allow these molecules to pass through the BSCB are also needed to develop them as drugs for the prevention and treatment of SCII. Current studies on the preventive and therapeutic use of miRNAs in SCII are at the animal experimentation phase, and no miRNA-based drugs are currently used clinically to treat SCII. Therefore, more preclinical research and clinical trials are required to investigate the use of non-coding RNAs in clinical situations.

Moreover, to date, the altered expression levels of miRNAs in blood samples or cerebrospinal fluid after SCII have not been studied. Special miRNAs with differential expression in blood or cerebrospinal fluid could potentially be used as novel biomarkers. Studies on the interactions between miRNAs and lncRNAs following SCII require further investigation. In addition, previous studies have not considered whether miRNAs are differentially expressed in microglia, oligodendrocytes, astrocytes, and neurons in the spinal cord. Exploring the functions of miRNAs under pathological and normal conditions in specific cell types would improve the efficacy and specificity of miRNA therapeutic strategies. Single-cell RNA-Seq analysis could help explore the roles of miRNAs with single-cell resolution and thus better understand their cell-specific mechanisms. In summary, future research should address these challenges by exploring how miRNAs exert their effects via downstream target genes, designing methods to decrease off-target effects, developing delivery methods and chemical formulations to help miRNAs cross the BSCB, and developing approaches to identify candidate miRNAs biomarkers. Clinically effective miRNA-based drugs and successful clinical trials are key goals in the development of this field.

In conclusion, SCII is a complex clinical problem that needs further study. Numerous studies have explored the pathogenesis of SCII and revealed the pathological changes that occur in this condition. miRNAs are considered to play an important regulatory role in SCII and may become potential targets for the prevention and treatment of SCII. Future studies focusing on the functional roles and detailed mechanisms of miRNAs are needed to develop targeted therapies for SCII.

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