

Non-Coding RNAs Regulate Spinal Cord Injury-Related Neuropathic Pain via Neuroinflammation

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Abstract: Secondary chronic neuropathic pain (NP) in addition to sensory, motor, or autonomic dysfunction can significantly reduce quality of life after spinal cord injury (SCI). The mechanisms of SCI-related NP have been studied in clinical trials and with the use of experimental models. However, in developing new treatment strategies for SCI patients, NP poses new challenges. The inflammatory response following SCI promotes the development of NP. Previous studies suggest that reducing neuroinflammation following SCI can improve NP-related behaviors. Intensive studies of the roles of non-coding RNAs in SCI have discovered that ncRNAs bind target mRNA, act between activated glia, neuronal cells, or other immunocytes, regulate gene expression, inhibit inflammation, and influence the prognosis of NP.

Keywords: non-coding RNAs, neuroinflammation, neuropathic pain, spinal cord injury

Introduction

Spinal cord injury (SCI) is often accompanied by major impairments in motor, sensory, and autonomic functions.¹ The molecular and biochemical pathways associated with the pathophysiology of SCI include intra-tissue hypoxia, oxidative stress, inflammation, apoptosis, and so on. SCI is classified as primary or secondary. Common symptoms of SCI include neuropathic pain (NP), spasticity, abnormal autonomic reflexes, and impairment of social, recreational, and occupational activities.² Primary SCI can trigger secondary SCI, resulting in further chemical and mechanical damage to tissues. A common secondary complication of SCI is NP, which patients usually experience spontaneously, abnormally, or with hypersensitivity to pain.³ Severe SCI-related NP is associated with decreased quality of life. Conventional treatments have difficulty resolving severe NP, and many clinical needs remain unmet. Despite the many therapeutic strategies proposed and various breakthroughs achieved, cure remains elusive, probably due to the complex healing and protective mechanisms involved.^{4–6}

Neuroinflammation (NI) is a coordinated response of the immune system against infection following SCI.⁷ In the past decade or so, NI following SCI was linked to intractable NP. Anatomical alterations associated with SCI include disruption of the blood-spinal cord barrier.^{8,9} During blood-spinal cord barrier disruption, immune cells will enter the spinal cord parenchyma and cause direct inflammation. Neurons, neutrophils, microglia, macrophages, astrocytes, and B and T lymphocytes, as well as cytokines contribute to this mechanistic process. SCI-induced NI produces NP and promotes NP-related behaviors.^{10–14} Disruption of the blood-spinal cord barrier and subsequent infiltration of leukocytes

induces central NI, as well as activation, migration, and proliferation of microglia and astrocytes, which can promote the production and release of inflammatory cytokines, including tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6, which have been associated with behavioral indicators of SCI-related NP.^{8,15–19} A growing body of evidence suggests that NI following SCI can prolong NP.⁷

Non-coding RNAs (ncRNAs), which include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), play important roles in regulation of gene expression in central nervous system. In this review, we discuss how ncRNAs expression changes are associated with SCI-related NP. Except for miRNAs, lncRNAs and circRNAs, NP is rarely associated with other types of ncRNAs, and these are not discussed here. Notably, ncRNAs do not code for proteins, but rather regulate the expression of genes and proteins involved in inflammatory and immune responses following SCI through a variety of mechanisms. For example, miRNAs regulate the proliferation of astrocytes to mediate NI, while lncRNAs and circRNAs act as sponges of RNAs or miRNAs during the progression of NP, regulate expression epigenetically of NP-related molecules or modulate procession of miRNAs.^{20–24}

The aim of this review article is to facilitate understanding of SCI-related NP by highlighting the etiological impact of ncRNAs and associations with cells and molecules involved in the pathophysiology of SCI as potential prognostic targets for SCI-related NP.

Epidemiology

Statistics show that the prevalence of NP ranges from 50.7% to 81% in patients with SCI.^{25–34} The International Association of the Study of Pain classifies SCI-related pain as nociceptive pain or NP.^{26,35} Among SCI patients, the incidence of nociceptive pain ranges from 40.6% to 59% and NP from 30.2% to 53%.^{5,25–27,32,36} Due to differences in the definition of pain, diagnostic tools, and study types, the prevalence of SCI-related NP widely varies.³⁷ Nociceptive pain presents as musculoskeletal pain, which is associated with pathological changes to the bones, joints, and/or muscles, resulting in pain of the arm or shoulder, or visceral pain of the abdomen involving renal calculus, bowel, and sphincter dysfunction.^{35,38,39} NP is classified as at-level or below-level. At-level NP is referred to as the dermatome, which at the level of neuropathic damage and/or within three dermatomes below the level of neurological damage due to disease or injury to the nerve root or spinal cord, whereas below-level NP refers to pain beyond three dermatomes below the level of neuropathic damage due to direct injury to the spinal cord.^{40,41} SCI-related NP could be spontaneous or stimulus-evoked, continuous or intermittent. SCI patients describe NP as burning, sharp, cramping, cold, squeezing, stinging, or electric shock-like.^{2,42,43} SCI-related NP is severe in hyperacute time and it mainly occurs in the at-level. Compared to the chronic phase, acute NP is reported as intense electric and cold stimulation that is more prevalent after 6 months. After 1 year, below-level NP starts to increase.^{5,44} The severity of NP can gradually increase and cause progressive damage to the spinal cord over time.^{45,46} SCI-related NP negatively influences quality of life via disruption of daily activities, sleep disorders/insomnia, and anxiety/depression.^{29,33} In addition, SCI-related NP may cause more disabling than physical damage and bring about a sense of isolation and despair.⁴⁷ Demographic variables related to NP include female sex, advanced age, and financial status.^{30,36,48} An analysis of clinical data in SCI-NP patients (spinal cord injury associated with neuropathic pain) showed significantly high TNF- α /IL-6 expression and a stronger association of TNF- α with NP in SCI patients.⁴⁹

Pathophysiological Roles of miRNAs, lncRNAs, and circRNAs in SCI-Related NP via Neuroinflammation

Inflammation-Linked miRNAs in SCI-Related NP

The mechanisms underlying SCI-related NP involve complex interactions among neuronal cells, glial cells, and non-neuronal cells. Most studies of the roles of miRNAs in SCI-related NP have focused on neurons, astrocytes, microglia, and macrophages. However, a previous study of the interactions of miRNAs in oligodendrocytes found that transplantation of precursor oligodendrocytes attenuated mechanical hypersensitivity reactions.⁵⁰ During SCI, miRNAs regulate the functions of cells involved in tissue repair and regeneration together with active participation in messaging to maintain neurological homeostasis. These comprehensive summaries of research findings are shown in Figure 1.

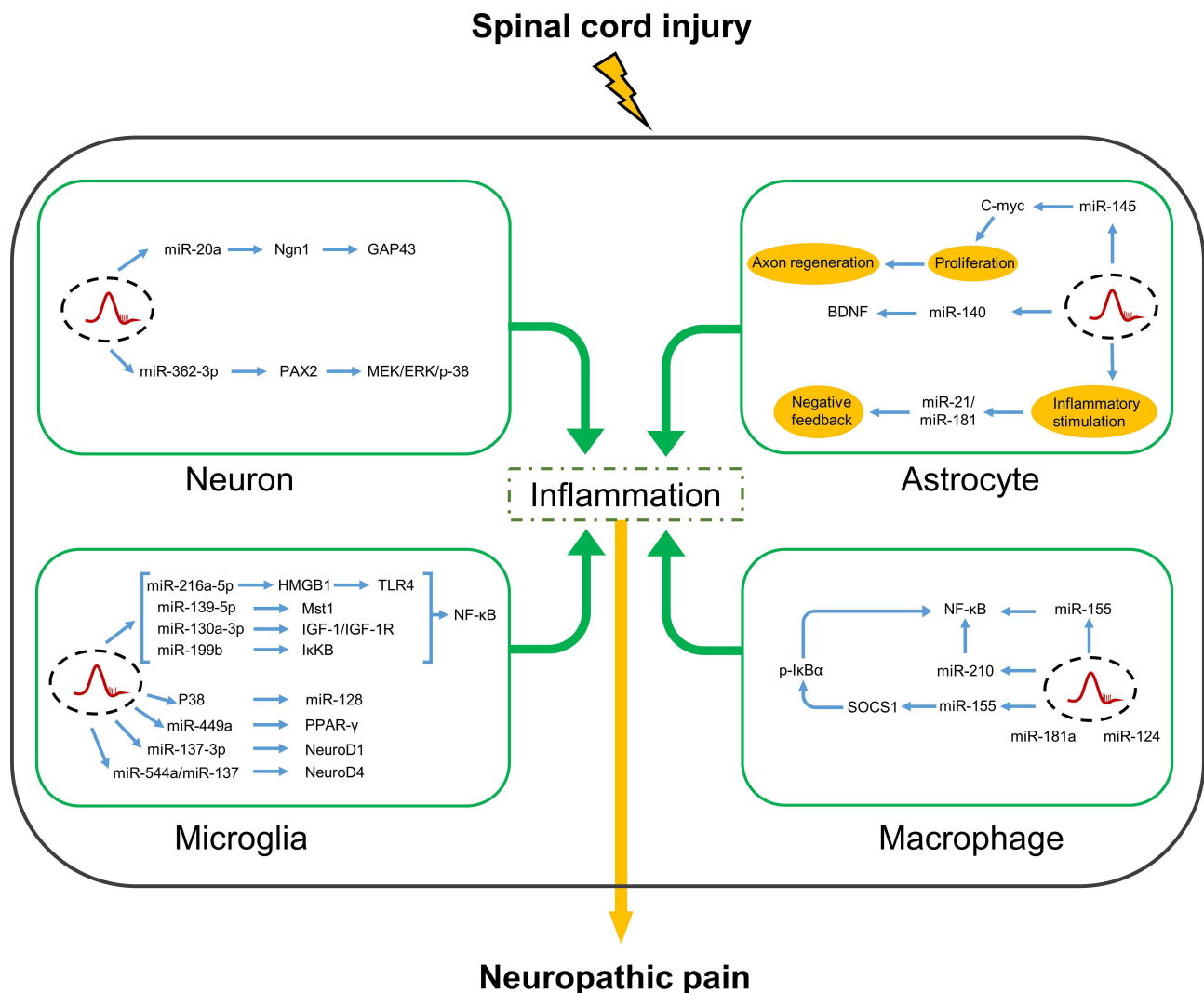


Figure 1 In neurons, microglia, astrocytes and macrophages, miRNAs regulate inflammatory factors by acting on various target genes after spinal cord injury, thereby relieving or worsening neuropathic pain.

Abbreviations: PAX2, pair box gene2; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal regulated kinases; NF-κB, nuclear factor kappa-B; p-38, p38 MAPK; MAPK, mitogen-activated protein kinases; GAP43, growth-associated protein 43; Ngn1, neurogenin-1; C-myc, V-Myc avian myelocytomatosis viral oncogene homolog; BDNF, brain-derived neurotrophic factor; PPAR-γ, peroxisome proliferator-activated receptor γ; IκKB, inhibitor of kappa B kinase β; NeuroD1, neuronal differentiation 1; NeuroD4, neuronal differentiation 4; Mst1, macrophage stimulating 1; HMGB1, high mobility group protein 1; TLR4, toll-like receptor 4; p-IκBα, phosphorylated NF-kappa-B inhibitor alpha; SOCS1, suppressor of cytokine signaling1.

Roles of miRNAs in Neuron-Mediated Inflammation

NP occurs after nerve injury and the noxious reaction of neurons may persist long after tissue repair, suggesting a possible association with altered neuronal function.⁵¹ Neuronal responses to SCI are mediated by miR-20a via multiple pathways. Injection of miR20a into the spinal cord caused abnormal expression of miR20a and induced secondary injury, targeting Ngn-1 together with downregulated regeneration-related functional gene GAP43, upregulating IL-6, TNF-α, COX-2, with invasive inflammation of the spinal cord after 2 days and influenced the activation of endogenous neural cell regeneration, whereas the miR-20a-PDZ-Rhogef/RhoA/GAP43 axis promoted recovery of superior sensory function and inhibited the formation of lesions of the dorsal spinal cord via miR-20a modulation in spinal cord dorsal column injury.^{52,53} Subsequent studies revealed the involvement of miR-362-3p in the regulation of brain-derived neurotrophic factors by targeting PAX2, where overexpression of miR-362-3p downregulated expression of IL-1β, TNF-α, COX-2, and IL-6, which suppressed neuronal inflammation, thereby treating SCI-related NP.⁵⁴ However, further studies are

needed to explore the functional mechanisms of these various molecules as potential therapeutic targets for SCI-related inflammation and NP.

Roles of miRNAs in Microglia Mediated Inflammation

Microglia and astrocytes of the central nervous system strongly enhance neuronal excitability in response to injury.⁵⁵ Microglia are quickly activated in response to harmful stimuli and directly express specific neurotransmitter receptors associated with NP and subsequently activate intracellular signaling pathways that promote the release of pro-inflammatory factors, such as TNF- α , IL-1 β /6, and nitric oxide, which play key roles in the induction of NP.^{56–58} Therefore, it is important to clarify the molecular mechanisms underlying microglia-induced inflammation for treatment of SCI-related NP.

Many miRNAs that influence microglia-mediated inflammation after SCI participate in the regulation of downstream target genes. A previous study reported a correlation between TUSC7 and miR-449a expression in a rat model of SCI, where overexpression of TUSC7 inhibited miR-449a, while upregulation of PPAR- γ inhibited microglia activation and decreased expression of the pro-inflammatory factors TNF- α and IL-1 β in the regulation of NP.⁵⁹ Moreover, upregulation of miR-137-3p directly reduced expression of TNF- α and IL-1 β via negative regulation of NeuroD1 in lipopolysaccharide (LPS)-treated BV2 cells (Gao et al, 2019).⁶⁰ Both miR-137 and miR-544a can also target NeuroD4 and down-regulate pro-inflammatory cytokines to reduce inflammation caused by spinal cord injury. Activation of the P38 signaling pathway, following the downregulation of miRNA-128 promotes the transformation of microglia from M1 to M2 which is involved in NP and improves spinal cord injury.⁶¹ Collectively, these findings suggest that miRNAs can significantly ameliorate SCI-related inflammation and NP.^{62,63}

It is well known that NF- κ B is closely related to immunity as a transcription factor, and its mediated signaling pathway is considered to be the regulator of cell homeostasis. The signaling pathway is divided into three parts: (1) ligand and receptor binding; (2) receptor-related signaling; (3) Transcriptional activation and biological function of downstream genes. Three categories of protein families in the NF- κ B pathway are the NF- κ B transcription factor family (mainly divided into p50 (NF- κ B1), p52 (NF- κ B2), RelA (p65), c-Rel, and RelB), I κ B family – an inhibitor of NF- κ B transcription activity, and I κ KB family – an inhibitor of I κ B protein activity eliminate the inhibition of NF- κ B. Under normal conditions, the inhibitory protein I κ B forms a complex with NF- κ B that inactivates NF- κ B.⁶⁴

Interestingly, NF- κ B-dependent inflammation is reported to cause neuropathic nociceptive hyperalgesia in a mouse model of peripheral nerve injury, in response to SCI, inflammatory cytokines, and other antigens bind to receptors, and the NF- κ B pathway is activated and involved in the immunomodulatory response caused by I κ B inhibited by I κ KB kinase.⁶⁵ However, after the administration of I κ KB inhibitors, the NF- κ B pathway was inhibited, which negatively secrete pro-inflammatory factors IL-16, CCL2, TNF- α , MCP-1, and narrow NI to help prevent the development of chronic nerve pain.⁶⁶ However, miRNAs can also modulate the inflammatory response by inhibiting activation of the NF- κ B signaling pathway. MiR-199b is reported to mediate activation of the I κ K β -NF- κ B signaling pathway in microglia, which attenuated inflammation in response to acute SCI, while overexpression of miR-199b reversed the upregulation of I κ K β resulting in the activity of p-p65 was inhibited and affected the microglia biological functions. MiR-216a-5p is reported to alleviate inflammation-related behaviors by inhibition of microglia-mediated inflammation via the HMGB1-TLR4-NF- κ B pathway. In addition, the miRNAs mediated NF- κ B signaling pathway plays a role in NP after spinal cord injury by regulating inflammatory responses. Upregulation of miR-216a-5p expression inhibits the activity of the p-65 transcription factor by targeting HMGB1 to bind to TLR4, thereby blocking the signaling pathway to reduce the inflammatory response and improve inflammatory pain. Thus, miR-216a-5p was proposed as a potential therapeutic target for SCI-related NP.^{67,68} A previous study demonstrated that miR-139-5P reduced expression levels of TNF- α and IL-1 β by targeting Mst1, which inhibited NF- κ B-related inflammatory responses and reduced nociceptive hypersensitivity, while downregulation of miR-130a-3p inhibited IGF-1 expression and reduced microglia activation by blocking NF- κ B phosphorylation, leading to decreased expression of IL-1 β , IL-6, and TNF- α , which significantly improved NP.^{69,70} These results confirm the important roles of miRNAs in NF- κ B-mediated inflammation in response to SCI-NP.

Roles of miRNAs in Astrocyte-Mediated Inflammation

Astrocytes adopt either a pro-inflammatory or anti-inflammatory phenotype.⁷¹ Under pathological conditions, activated astrocytes adopt an anti-inflammatory phenotype to protect the central nervous system against NI.^{72,73}

For days to weeks after spinal cord injury (SCI), the proliferation and hypertrophy of astrocytes may be involved in the lesion site, inducing glial scar formation. In response to SCI, miR-146a expression is upregulated in spinal cord astrocytes. Although miR-146a was highly expressed in spinal cord astrocytes after spinal cord injury, it has anti-inflammatory properties and plays a part in inducing glial scar hyperplasia.⁷⁴ An in vitro model of LPS-induced glial cell injury revealed that MiR-140 not only inhibited expression of BDNF but also downregulated expression of IL-6 and TGF- α by binding to the 3'-untranslated region of BDNF.⁷⁵

In a mouse model of LPS-induced inflammation, downregulation of miR-181 enhanced astrocyte production of the pro-inflammatory cytokines TNF- α , IL-6, IL-1 β , and IL-8, while overexpression of miR-181 significantly increased expression of the anti-inflammatory cytokine IL-10.⁷⁶ An in vitro study proposed GFAP and c-Myc as potential targets of miR-145 in astrocytes and found that miR-145 expression was downregulated in astrocytes in response to LPS-induced inflammation. However, overexpression of astrocyte-specific miR-145 decreased the density, size, and number of protrusions of astrocytes, suggesting that the inflammatory signaling pathways activated by SCI may promote the proliferation of astrocytes via inhibition of miR-145 expression.⁷⁷ In rat models of chronic compression injury and spinal nerve ligation, NP was associated with miR-21 and miR-21 expression was upregulated in neurons and astrocytes in the chronic phase of SCI, especially affecting astroglial cell proliferation to form scarring.^{78–80} The regulatory sequence of miR-21 contains a highly conserved 300-bp region consisting of two STAT3-binding sites.⁸¹ Ablation of STAT3 limited early intrapathological hypertrophy of astrocytes and increased inflammatory cell invasion in response to SCI.⁸² Nonetheless, further studies are warranted to confirm the link between miR-21 and SCI-related NP.⁸³

Roles of miRNAs in Macrophage-Mediated Inflammation

Macrophages from the peripheral circulation and resident microglia of the central nervous system are among the major effector cells that participate in SCI-related inflammation.⁸⁴ Macrophages play an important role in the early inflammatory response via production of various pro-inflammatory cytokines and chemokines, which activate specific signaling pathways that trigger the production of other cytokines to further recruit more macrophages, ultimately leading to NP and disease progression.⁸⁵

In a rat model of SCI, miR-124 reduced inflammation of the CNS by inhibiting the recruitment of macrophages and monocytes.⁸⁶ In macrophages, miR-181a can directly downregulate IL-1 α levels to regulate the inflammatory response.⁸⁷ Since miR-181 is an important anti-inflammatory factor, reduced expression of miR-181 could increase SCI-related inflammation.⁷⁴ Moreover, as a negative feedback regulator of an inflammatory response, miR-210 targeting NF- κ B1 reduces inflammatory levels by inhibiting I κ B kinase activity, which is manifested by decreased expression of pro-inflammatory cytokines, including IL-6 and TNF- α , in endotoxin-induced macrophages.⁸⁸ AgomiR-210 is a chemically modified miRNA agonist that is reported to mediate inflammation in a rat model of SCI. Together, these findings suggest the importance of the regulatory role of miR-210 in SCI-related NI.⁸⁹

Human miR-155 has been implicated in stem cell differentiation, immunity, inflammation, cancer, and other pathophysiological processes.⁹⁰ The use of a chronic compression injury model of NP demonstrated that inhibition of miR-155 significantly reduced mechanical and thermal hypernociception and inhibited macrophage production of pro-inflammatory cytokines and NF- κ B and p38 MAPK activity via SOCS1.⁹¹ Thus, miR-155 presents a potential therapeutic target for SCI-related NP, although further studies are needed to clarify the underlying mechanism.⁹²

Inflammation-Linked lncRNAs in SCI-Related NP

Recent studies have revealed that lncRNAs are involved in various physiological and pathological processes, including adipogenesis, bone development, tumor formation, diabetes, and neurological diseases.^{93–97} The biological functions of lncRNAs mainly include chromatin regulation, transcription, and translation. Although initially considered

untranslatable, lncRNAs contain open reading frame sequences with translational functions.⁹⁸ The development of microarray and sequencing technologies has allowed investigations of the roles of lncRNAs in SCI-related inflammation and NP.

A mouse model of SCI showed that lncRNA *Neat1* was regulated by miR-124 and promoted neuronal differentiation and migration and inhibited apoptosis via the Wnt/ β -catenin signaling pathway, thus contributing to recovery from SCI.⁹⁹ Interestingly, *Neat1* increased expression of the inflammatory factors IL-6 and CXCL10, enhanced inflammasome activation, and promoted cellular scorching in vivo.^{100,101} In addition, *Neat1* is reported to directly target the miR-128-3p/AQP4 axis to modulate SCI-related inflammation and NP.¹⁰² Meanwhile, knockdown of *NEAT1* inhibited expression of IL-6, IL-1 β , TNF- α , and AQP4, whereas inhibition of miR-381 restored expression levels. In a rat model of SCI, lncRNA *PVT1* was reported upregulated and acted as a competing endogenous RNA that suppressed expression of miR-186-5p, thereby increasing CXCL13/CXCR5 expression and NP.¹⁰³ Surprisingly, the novel lncRNA *PKIA-AS1* enhanced promoter activity of CDK6 by reducing DNMT1-catalyzed methylation.¹⁰⁴ In addition, lncRNA *PKIA-AS1* has been identified as a key regulator of nerve injury-induced NP.

Small nucleolar RNA host genes (SNHG) are a recently discovered family of lncRNAs that are closely related to tumor formation. The lncRNAs SNHG6 and SNHG17 can promote the development and metastasis of colorectal cancer.^{105,106} SNHG family members also play important roles in SCI-related inflammation and NP. Inhibition of KLF4, which is upregulated in SCI, reduces expression of pro-inflammatory cytokines and inhibits activation of microglia.^{107,108} KLF4 was also shown to directly target lncRNA SNHG5, which promotes progression of SCI by increasing activities of astrocytes and microglia.^{109,110}

In a rat model of SCI, upregulation of lncRNA SNHG1 influenced the degree of NP via regulation of CDK4.¹¹¹ Meanwhile, lncRNA SNHG12 has been associated with SCI-related inflammation and NP. In a rat model of spare nerve injury, silencing of lncRNA SNHG12, which was upregulated in the dorsal root ganglia, attenuated NP and reduced expression of the inflammatory factors IL-1 β , IL-6, and TNF- α via upregulation of miR-494-3p.¹¹²

Inflammation-Linked circRNAs in SCI-Related NP

Among the known ncRNAs, circRNAs have been widely studied in various cancers, cardiovascular diseases, and diseases of the central nervous system, where these molecules mainly function as sponges for miRNAs and RNA-binding proteins, and can drive translation through internal ribosomal entry sites and N6-methyladenosine sites.¹¹³ However, further studies are needed to clarify the differential expression of circRNAs before and after SCI.

Numerous studies have shown that circRNAs play crucial roles in SCI-related NP. For instance, circPrkcs is reportedly upregulated in astrocytes and microglia in response to SCI and acts as a sponge to competitively inhibit expression of miR-488.^{114,115} Knockdown of circPrkcs can reduce CCL2 expression in astrocytes and regulate the MEK1/JNK/p38 MAPK pathway via upregulation of miR-488 in microglia, thereby improving SCI-related inflammation. KLF4 was identified as a key regulator of SI-related NI. In a mouse model of traumatic SCI at T8–10, miR-135b-5p was significantly downregulated.¹¹⁶ KLF4 and circAbca1 have been identified as targets of miR-135b-5p and the circAbca1/miR-135b-5p/KLF4 axis was found to regulate progression of traumatic SCI. Both circ0001723 and circ003564 were closely associated with NLRP3 expression after SCI.^{117,118} Inhibition of the NLRP3 inflammasome is reported to reduce SCI-related NI and mitochondrial dysfunction, thereby limiting the extent of SCI.¹¹⁹ In a mouse model of SCI, circUsp10 was found to regulate activation of microglia via the miR-152-5p/CD84 axis.¹²⁰ Similarly, exosome-mediated circZFHX3 enhanced microglia viability and subsequently exacerbated inflammation-induced secondary injury.¹²¹

The NF- κ B signaling pathway has been implicated in the pathology of NI, neural regeneration, cellular scorching, and disruption of the blood-spinal cord barrier after SCI. In addition, circ0000962, circ014301, circHecw1, and circNcam2 were shown to regulate SCI-related NI via the NF- κ B pathway. Expression of circ0000962 is downregulated after SCI and overexpression of circ0000962 was shown to reduce expression of TNF- α , IL-1 β , IL-6, and IL-18 via downregulation of miR-302b-3p and regulation by the PI3K/Akt/NF- κ B signaling pathway.¹²² An in vitro model of SCI based on LPS-treated PC12 cells found that circHecw1 regulated expression of inflammatory factors via miR-3551-3p and NF- κ B.¹²³ Meanwhile, circRNA_014301 was found to regulate inflammation and apoptosis of PC-12 cells by upregulation of

p-NF- κ B/NF- κ B, Bax, and cleaved caspase-3, and downregulation of Bcl-2.¹²⁴ Silencing of circ-Ncam2 induced miR-544-3p expression, which inhibited activation of the TLR4/NF- κ B pathway, reduced activation of LPS-treated microglia, and inhibited neuronal apoptosis, thereby promoting recovery from SCI.¹²⁵

In a rat model of diabetes, circHIPK3 negatively regulated miR-124 expression and knockdown of circHIPK3 attenuated NI-related NP.¹²⁶ On day 7 post SCI of rats, circRNA-2960 was significantly upregulated in tissues around the surgical site.¹²⁷ Interestingly, circRNA-2960 was found to target and downregulate miR-124, which exacerbated the inflammatory response, similar to diabetes-induced NP, suggesting that the circRNA-2960/miR-124 complex is a potential target for treatment of SCI-related NP. A comprehensive summary of these findings is shown in Figure 2.

Although there are not many reports of circRNAs mediating SCI-related inflammation and NP via the NF- κ B pathway, several studies have confirmed that the NF- κ B pathway is closely associated with inflammation and NP following SCI. For example, combination therapy with minocycline and botulinum toxin can reduce SCI-induced NP and inflammation by activation of SIRT1 and inhibition of pAKT, P53, and p-NF- κ B.¹²⁸ SAFit2, an inhibitor of FKBP51,

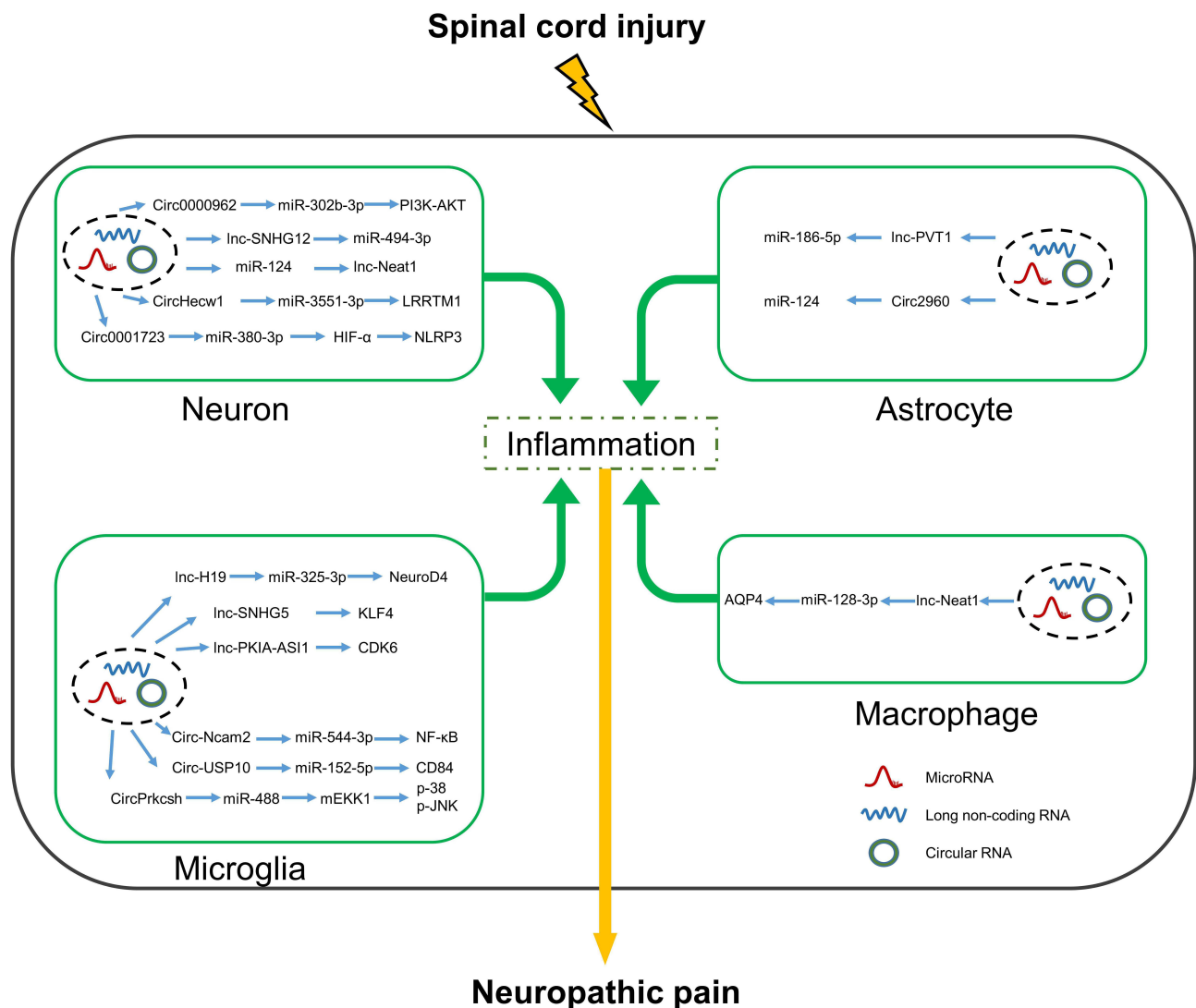


Figure 2 Interactions between lncRNAs/CircRNAs and miRNAs in neurons, microglia, astrocytes and macrophages alter the expression of inflammatory factors that affect neuropathic pain after spinal cord injury.

Abbreviations: HIF- α , hypoxia-inducible factor-1 α ; PI3K, phosphoinositide 3-Kinase; AKT, protein kinase B; LRRTM1, leucine-rich repeat transmembrane neuronal protein 1; NLRP3, nod-like receptor thermal protein domain associated protein 3; CDK6, cyclin-dependent kinase 6; KLF4, kruppel-like factor 4; mEKK1, MAPK/ERK kinase kinase 1; p-38, p38 MAPK; MAPK, mitogen activated protein kinases; p-JNK, jun n terminal kinase phosphorylated; NeuroD4, neuronal differentiation 4; CD84 (SLAMF5), signaling lymphocytic Activation Molecule Family 5; AQP4, aquaporin-4.

inhibits activation of the NF- κ B pathway and reduces expression of inflammatory factors in the dorsal root ganglia and spinal cord to improve NP caused by nerve injury.¹²⁹

Treatments

SCI-induced activation of the immune system is involved in tissue damage and repair, and activation of the inflammatory responses affects the prognosis of SCI-related NP. Recent studies have found that various miRNAs play essential roles in SCI-related inflammation and NP. Thus, the therapeutic roles of miRNAs have received much attention. Delivery of miRNA-124a via a chitosan multimeric system reduced microglia activation and TNF- α in vitro in a rat model of SCI, thereby providing a promising therapeutic approach for delivery of miRNAs.⁸⁶

Several neuroprotective agents have been tested for treatment of SCI, including curcumin.^{60,130} A recent study of BV2 cells treated with curcumin found that LPS-induced inflammation was reduced via upregulation of miR-137-3p and downregulation of NeuroD1.⁶⁰ In an in vivo study of SCI-related NP, miR-362-3p increased expression of TNF- α and IL-6 in neurons. Clinical data showed that SCI-NP is highly associated with TNF- α as a potential diagnostic biomarker in SCI patients. Recently, a TNF- α lentiviral shRNA vector relieved NP via TNF- α inhibition of downstream IL-6 expression, as a novel therapeutic option for NP.^{49,131}

Perspectives and Conclusion

NP is a serious complication of SCI that negatively impacts quality of life and prognosis. Therefore, ncRNAs continue to attract attention for SCI-related NP. Our understanding of NP induced by spinal cord injury-mediated NI continues to advance. Researchers have tried a number of solutions in order to deliver ncRNAs into cells. Cui et al and Jee et al attempted to use intramyelin lentivirus injection in animal models, and Qi et al mostly used cell transfection to regulate the expression of ncRNAs in cell models.^{53,86,99} Louw et al found a cell selector-specific chitosan complex vector, miR-124 can be injected more stably in vivo and in vitro, while lncRNA and circRNA have not been found to have such more stable delivery system, and special materials such as nano-encapsulated materials can be considered as carriers.

Immune cells take on different roles during different phases of SCI, neurons respond to spinal cord injury, microglia are activated, and astrocyte proliferation promotes the repair of injured lesion sites but may also affect axon repair due to hyperplasia of glial scars, which is important to consider the duration of effect.⁸⁰ Most commercially available reagents are now not cell type-specific, ensuring that targeted delivery of ncRNAs into cells and tissues to affect disease states without interfering with gene expression in other cells warrants consideration.

At present, gene therapy is gradually used in the clinical practice of various diseases. Recombinant adeno-associated virus (rAAV) is commonly used as a stable vector for gene delivery and is non-toxic and cannot be integrated into the human genome. Gene therapy would be a promising treatment approach, which can be used as gene vectors for ncRNAs to solve SCI-NP via NI, by silencing and increasing the regulation of pro-inflammatory and anti-inflammatory mediators. Further in-depth studies are warranted to explore the clinical application of ncRNAs for the treatment of SCI-related NP.

This review summarizes the mechanistic pathways mediated by non-coding RNAs, NI, and NP, indicating that the regulation of NI by non-coding RNAs is a potential target and direction for the treatment of secondary neuropathic pain after spinal cord injury in the future.

Materials and Methods

We searched the online databases of NCBI Medical Database (PubMed), Web of Science, SpringerLink, Elsevier (ScienceDirect), OVID series of Medical Databases, and Open Access Library Databases for all valuable literature by manual search. To better control quality, articles published in all journals are subjected to a rigorous screening process. Keywords include non-coding RNAs, neuroinflammation, neuropathic pain, and spinal cord injury, and we searched highly relevant articles for a detailed research strategy. Conventional searches were supplemented by manual searches of all the relevant studies, review articles, and conference abstracts to avoid losing papers that might have been missed. We have no restrictions on the year and country of publication in our search.

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Disclosure

The authors declare that they have no conflicts of interest.

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