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REVIEW

# Interactions Among lncRNAs/circRNAs, miRNAs, and mRNAs in Neuropathic Pain

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## Abstract

Neuropathic pain (NP) is directly caused by an injury or disease of the somatosensory nervous system. It is a serious type of chronic pain that is a burden to the economy and public health. Although recent studies have improved our understanding of NP, its pathogenesis has not been fully elucidated. Noncoding RNAs, including lncRNAs, circRNAs, and miRNAs, are involved in the pathological development of NP through many mechanisms. In addition, extensive evidence suggests that novel regulatory mechanisms among lncRNAs/circRNAs, miRNAs, and mRNAs play a crucial role in the pathophysiological process of NP. In this review, we comprehensively summarize the regulatory relationship among lncRNAs/circRNAs, miRNAs, and mRNAs and emphasize the important role of the lncRNA/circRNA–miRNA–mRNA axis in NP.

**Key Words** Noncoding RNA · neuropathic pain · function · mechanism · review.

## Introduction

Neuropathic pain (NP) is a worldwide problem that can be caused by a lesion or disease of the somatosensory system [1, 2]. Based on a systematic review of NP epidemiological studies, estimates of NP prevalence range from 6.9 to 10% [3]. The 2 causes of NP [4, 5] have been confirmed to be central nerve injury (such as stroke, multiple sclerosis, and spinal cord injury [SCI]) and peripheral nerve injury (PNI) (such as diabetes mellitus, peripheral nerve compression, and postherpetic neuralgia). The prevalence of central NP and peripheral NP has increased because of the growing elderly population worldwide [1]. NP leads to serious pain, sleep disorders, impaired quality of life, anxiety, and depression [6], which can lead to economic burden, including direct expenses (such as healthcare expenditures) and indirect expenses (such as sick leave) [7, 8]. In Europe, the direct and indirect expenses (indirect expenses percentage in total expenses) of NP per patient were €9685 in the UK (57%), €10,597 in Spain (67%), €9305 in Italy (69%), €14,446 in Germany (78%), and €10,313 in France (69%) [8].

The mechanism of NP involves multiple organs and systems, such as the sciatic nerve, dorsal root ganglia (DRG), spinal cord, and brain [5, 9, 10]. Moreover, numerous NP mechanisms have been discovered in animal studies. Animal models of NP are conducted by surgical lesions of PNI and central nerve injury, such as the constriction, ligation, and transection of nerves [1]. The common animal models of NP are SCI, spared nerve injury (SNI), sciatic nerve chronic constriction injury (CCI), partial sciatic nerve ligation, chronic compression of the DRG, and spinal nerve ligation (SNL) [11–13]. Although some mechanisms of NP are well discovered, it remains difficult to prevent and treat NP without thoroughly illuminating the underlying mechanisms. Finding novel biomarkers for diagnosis and therapeutic targets of NP is important to develop more effective treatment programs. In recent decades, many studies have revealed the role of noncoding RNAs (ncRNAs) in the development and progression of NP [14, 15].

The discovery of ncRNAs brought novel landscapes for the diagnosis and treatment of NP. ncRNAs are not translated into proteins; they are functional small RNA molecules. Only 2% of the human genome consists of protein-coding genes, and approximately 98% of the rest are noncoding genes [16]. Currently, the ncRNAs mainly include microRNAs (miRNAs), long ncRNAs (lncRNAs), circular RNAs

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(circRNAs), and small nucleolar RNAs (snoRNAs) [17]. Numerous studies [18–20] have highlighted that miRNAs, lncRNAs, and circRNAs are pertinent to the pathological processes of NP, such as inflammation. In addition, many studies have focused on the interactions among lncRNAs/circRNAs, miRNAs, and messenger RNAs (mRNAs). The lncRNAs and circRNAs have a cross-talk with miRNAs and then regulate mRNA expression in the progression of NP. In this review, we elaborate the roles of miRNAs, lncRNAs, and circRNAs in NP and highlight the role of the lncRNA/circRNA–miRNA–mRNA axis in the processes of NP.

## miRNAs and NP

miRNAs are small noncoding RNAs that were first reported in *Caenorhabditis elegans* in 1993. Lee and his colleagues revealed that the *C. elegans*-related gene lin-4 develops into 2 small RNAs instead of a protein [21, 22]. The length of miRNAs is approximately 21 to 25 nucleotides, and the target site of miRNAs is located in the 3′-untranslated region of mRNAs [23]. miRNAs are able to posttranscriptionally modulate gene expression via translation inhibition or mRNA degradation. When an miRNA is perfectly bound to the 3′-untranslated regions, the target mRNA degrades immediately; however, if the 2 species do not completely bind, then the miRNA will suppress the translation of the target mRNA [22, 24].

Under the development of bioinformatics, more than 1000 miRNAs have been detected in the human genome, and over 30% of the human genome may be modulated by these miRNAs [22, 25]. miRNAs participate in manifold biological regulation processes, including cell proliferation, differentiation, inflammation, and apoptosis [26–29]. Abundant evidence shows that miRNAs, as crucial regulators, participate in many pathological processes of human diseases, such as cancer [30], cardiac diseases [31], and diabetes [32]. Studies have shown the dysregulation of miRNAs in the animal models of NP, suggesting that miRNAs play a crucial part in the development of NP. Zhou et al. [15] used a sequencing technique to detect differences in the miRNA expression profiles in the spinal cord between an SNI group and a control group. Based on the sequencing results, the SNI group had 6 upregulated and 6 downregulated miRNAs at 14 days after injury compared with the control group. Among the 12 differential miRNAs, miR-344b-1-3p and miR-490-3p were verified by quantitative polymerase chain reaction (qPCR). Chang and his colleagues [33] assessed the expression of differential miRNAs in the DRG of rats via microarray analysis. Compared with the sham group, 83 differential miRNAs (49 upregulated and 35 downregulated) in the SNL group were observed 7 days after nerve injury. In addition, the authors validated the expression of miR-21, miR-31, miR-668, and miR-672 in the DRG through qPCR and predicted the potential signaling pathways regulated by the 4 miRNAs.

It has been reported that the reduction of 40 to 68% of the miR-183 family, including the miR-183/96/182 cluster, in the DRG is sufficient to significantly alter gene expression. Of the NP-induced pain genes, 80% are modulated by the miR-183 family, indicating that the miR-183 family plays a vital role in the maintenance of NP [34]. Several studies showed that the expression of miR-183 was significantly downregulated in CCI or SNL rat models, and the overexpression of miR-183 was able to relieve pain-like behavior by inhibiting the target genes of miR-183 [35–38]. MiR-96 and miR-182 were also decreased in the NP rat model. Cai et al. [39] found that miR-182 was significantly decreased in the DRG of SNI rats, and sodium channel 1.7 (Nav1.7) expression was elevated, causing mechanical hyperalgesia. The injection of miR-182 agomir reversed the overexpression of Nav1.7 and could restrain mechanical allodynia caused by NP. Similarly, several studies [34, 40] also reported that in NP animal mods, the expression of miR-96 was greatly downregulated in the DRG. Moreover, Cai et al. [41] reported that CCI caused miR-150 downregulation in the dorsal spinal cord at 7 days. AKT3 was directly targeted by miR-150 and upregulated in CCI rats. The overexpression of miR-150 could suppress the impacts of AKT3 and significantly relieve NP in CCI rats. Another study [42] found that miR-34a was significantly downregulated in the DRG at 12 days after CCI, with a significant reduction in the pain threshold. A luciferase assay was used to prove that vesicle-associated membrane protein 2 (VAMP-2) and voltage-gated sodium channel β2 subunit (SCN2B) were the target genes of miR-34a, which were confirmed by enzyme-linked immunosorbent assay. However, VAMP-2 expression was greatly enhanced, whereas SCN2B expression was only marginally altered, showing that the miR-34a/VAMP-2 pathway was possibly relevant to NP. Accumulating evidence has emphasized that the induction and maintenance of NP are accompanied by changes in the expression of miRNAs, and detailed information about these miRNAs is shown in Table 1.

## lncRNAs and NP

In the late 1980s, scientists discovered the first noncoding RNA, H19, but at that time, such RNA was considered mRNA [94]. Subsequently, another study reported that H19 was unusual compared with other mRNAs because the gene was not involved in translation, although it contained an open reading framework. Scientists suggested that H19 was an RNA molecule [95] until the early 1990s, when H19 was widely investigated as an lncRNA and then regarded as a prototype for manifold lncRNAs. lncRNAs are RNA molecules with greater than 200 nucleotides in length and that may

**Table 1** Functional characterization of the miRNAs in NP

| miRNA | Expression | Target gene(s) | Model | Region | Functions | Reference |
|---|---|---|---|---|---|---|
| miR-21 | Up | CCL1, TIMP3 | CCI rat model | Spinal cord | Neuroinflammation | [43] |
| | | IL-1β | SNL/CCI rat model | DRG | Neuroinflammation | [44] |
| miR-195 | Up | Patched1 | CCI rat model | Cerebrospinal fluid | Neuroinflammation | [45] |
| | | ATG14 | SNL rat model | Spinal cord, microglia | Neuroinflammation | [46] |
| miR-155 | Up | SGK3 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [47] |
| | | SOCS1 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [48] |
| miR-34c-5p | Up | SIRT1, STAT3 | CCI rat model | Spinal cord, DRG | Neuroinflammation | [49] |
| miR-192-5p | Up | XIAP | SNI rat model | Spinal cord | Apoptosis | [50] |
| miR-15a/16 | Up | GRK2 | CCI rat model | Spinal cord | Neuroinflammation | [51] |
| miR-217 | Up | TLR5 | bCCI rat model | Spinal cord | Neuroinflammation | [52] |
| miR-32-5p | Up | Dusp5 | SNL rat model | Spinal cord, microglia | Neuroinflammation | [53] |
| miR-218 | Up | SOCS3 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [54] |
| miR-132-3p | Up | GluA1, GluA2 | SNI rat model | Spinal cord, DRG, microglia | Neuronal plasticity | [55] |
| miR-221 | Up | SOCS1 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [56] |
| miR-19a | Up | SOCS1 | CCI rat model | Spinal cord | Neuroinflammation | [57] |
| miR-183 | Down | MAP3K4 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [35] |
| | | mTOR/VEGF | CCI rat model | Spinal cord, PC12 cell | Neuroinflammation | [36] |
| | | TREK-1 | CCI rat model | DRG | Neuronal excitability | [37] |
| | | Nav1.3, BDNF | SNL rat model | DRG | Neuronal excitability | [38] |
| miR-182 | Down | Nav1.7 | SNI rat model | DRG | Neuronal excitability | [39] |
| miR-96 | Down | Nav1.3 | CCI rat model | DRG | Neuronal excitability | [40] |
| miR-96/182/183 | Down | – | SNL rat model | DRG | – | [34] |
| miR-150 | Down | AKT3 | CCI rat model | Spinal cord | Neuroinflammation | [41] |
| | | TLR5 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [58] |
| miR-7a | Down | NEFL, STAT3 | SNL rat model | DRG | Neuronal excitability | [59] |
| | | Scn2b | SNL rat model | DRG | Neuronal excitability | [60] |
| miR-206 | Down | HDAC4 | CCI rat model | DRG | Neuronal excitability | [61] |
| | | BDNF | CCI rat model | DRG, PC12 cell | Neuroinflammation | [62] |
| miR-30b | Down | Nav1.3 | SNL rat model | Spinal cord, DRG neuron | Neuronal excitability | [63] |
| | | Nav1.7 | SNI rat model | DRG, PC12 cell | Neuronal excitability | [64] |
| miR-194 | Down | FOXA1 | CCI rat model | Spinal cord | Neuroinflammation | [65] |
| miR-384-5p | Down | SCN3A | CCI rat model | DRG | Neuroinflammation | [66] |
| miR-15a | Down | AKT3 | CCI rat model | Spinal cord, PC12 cell | Autophagy | [67] |
| miR-144 | Down | RASA1 | CCI mice model | DRG | Neuroinflammation | [68] |
| miR-138 | Down | NF-κB | SNI mice model | Spinal cord | Neuroinflammation | [69] |
| miR-34a | Down | SCN2B, VAMP-2 | CCI rat model | DRG | Neuroinflammation | [42] |
| miR-340-5p | Down | Rap1A | CCI rat model | Spinal cord, microglia | Neuroinflammation | [70] |
| miR-202 | Down | Rap2A | CCI rat model | Spinal cord, PC12 cell | Neuronal plasticity | [71] |
| miR-98 | Down | HMGA2 | CCI rat model | Spinal cord | Neuroinflammation | [72] |
| miR-124-3p | Down | EZH2 | CCI rat model | Spinal cord | Neuroinflammation | [73] |
| miR-20b-5p | Down | AKT3 | CCI rat model | Spinal cord, PC12 cell | Neuroinflammation | [74] |
| miR-34c | Down | NLRP3 | CCI mice model | Spinal cord | Neuroinflammation | [75] |
| miR-20a | Down | PDZ-RhoGEF, RhoA, GAP43 | SDCL rat model | DRG | Sensory conduction | [76] |
| miR-152 | Down | MafB | PNI mice model | Spinal cord | Neuronal plasticity | [77] |
| miR-129-5p | Down | HMGB1 | CCI rat model | Spinal cord | Neuroinflammation | [78] |
| miR-214-3p | Down | DNMT3a, CSF1 | SNL rat model | DRG | Neuroinflammation | [79] |
| miR-362-3p | Down | PAX2 | SCI rat | Spinal cord | Neuroinflammation | [80] |
| miR-28-5p | Down | Zeb1 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [81] |
| miR-26a-5p | Down | MAPK6 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [82] |

**Table 1** (continued)

| miRNA | Expression | Target gene(s) | Model | Region | Functions | Reference |
|---|---|---|---|---|---|---|
| miR-93 | Down | STAT3 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [83] |
| miR-539 | Down | NR2B | CCI rat model | Brain | Neuronal plasticity | [84] |
| miR-449a | Down | TRPA1, KCNMA1, TPTE | SNI rat model | DRG | Neuronal excitability | [85] |
| miR-142-3p | Down | HMGB1 | SNL mice model | DRG, DRG neuron | Neuroinflammation | [86] |
| miR-200b/429 | Down | ZEB1 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [87] |
| miR-143 | Down | DNMT3a | SNL rat model | DRG | DNA methylation | [88] |
| miR-145 | Down | RREB1, p-AKT | CCI rat model | Spinal cord | Neuroinflammation | [89] |
| miR-141 | Down | HMGB1 | CCI rat model | DRG | Neuroinflammation | [90] |
| miR-1 | Down | BDNF, Cx43 | CCI rat model | Sciatic nerve | Neuroinflammation | [91] |
| miR-203 | Down | Rap1A | CCI rat model | Spinal cord, PC12 cell | Neuronal plasticity | [92] |
| miR-103 | Down | Cav1.2 | SNL rat model | Spinal cord, spinal neuron | Neuronal excitability | [93] |

CCI = sciatic nerve chronic constriction injury; SNL = sciatic nerve ligation; SNI = spared nerve injury; bCCI = bilateral sciatic nerve chronic constriction injury; SDCL = spinal cord dorsal column lesion; PNI = peripheral nerve injury; DRG = dorsal root ganglia; CCL1 = chemokines C-C motif ligand 1; TIMP3 = tissue inhibitor of metalloproteinase-3; IL-1β = interleukin-1β; SGK3 = serum and glucocorticoid–regulated protein kinase 3; SOCS = suppressor of cytokine signaling; SIRT1 = sirtuin-1; STAT3 = signal transducer and activator of transcription 3; XIAP = X-linked inhibitor of apoptosis protein; GRK2 = G protein-coupled receptor kinase 2; TLR5 = toll-like receptor 5; Dusp5 = dual-specificity phosphatase 5; SOCS3 = suppressor of cytokine signaling 3; GluA = AMPA receptor subunit; BDNF = brain-derived neurotrophic factor; NEFL = neurofilament light polypeptide; HDAC4 = histone deacetylase 4; FOXA1 = Forkhead box protein A1; RASA1 = RAS P21 Protein Activator 1; NF-κB = nuclear factor-κB; SCN2B = voltage-gated sodium channel β2 subunit; VAMP-2 = vesicle-associated membrane protein 2; Rap1A = Ras-related protein 1A; HMGA2 = high mobility group A2; NLRP3 = nucleotide binding domain-like receptor protein 3; HMGB1 = high mobility group protein B1; DNMT3a = DNA methyltransferase 3a; CSF1 = colony-stimulating factor-1; PAX2 = paired box gene 2; ZEB1 = zinc finger E-box-binding homeobox 1; MAPK = mitogen-activated protein kinases; TRPA1 = transient receptor potential cation channel subfamily A member 1; KCNMA1 = calcium-activated potassium channel subunit α-1; TPTE = transmembrane phosphatase with tension homology; RREB1 = ras responsive element binding protein 1; p-AKT = phosphorylated protein kinase B; Cx43 = Connexin 43

or may not have a minor protein-coding function. On the basis of genomic location, lncRNAs could fall into 5 categories, namely, 1) sense, 2) anti-sense, 3) bidirectional, 4) intronic, and 5) intergenic. Recent research has shown that lncRNAs play crucial roles in biological processes, including cell growth, apoptosis, transcription, translation, cell differentiation, and immune responses, via various regulatory mechanisms, including the modulation of gene expression under specific conditions, DNA methylation, histone modification, sponging miRNAs, the modulation of mRNA stability, and the collection of transcription factors [96–99].

lncRNAs could play a crucial role in neuronal activity and injury through the control of nervous system development and synaptic plasticity and the deregulation of varying neurological and mental states [96]. Recently, considerable evidence has shown that lncRNAs are crucial players in NP processes. Microarray or RNA sequencing technologies have been applied to detect different lncRNA expression profiles in NP. Zhou and his colleagues [100] utilized second-generation RNA sequencing to detect lncRNA profiling in the SNI rat model and control rats. They discovered that the amount of differentially expressed lncRNAs peaked on the 7th day after SNI, and 25 lncRNAs were found to be upregulated and 101 downregulated in SNI rats compared with control rats at 7 days. Subsequently, 4 upregulated lncRNAs (XLOC_041439, Mlxipl, XLOC_022312 and LOC100911498) and 3 downregulated lncRNAs (Rn50_X_0739.1, XLOC_001451, and XLOC_026060) were validated by qPCR. Du et al. [101] found that compared with the control group, 1481 differential lncRNAs (1026 upregulated and 455 downregulated) and 1096 differential mRNAs (463 upregulated and 633 downregulated) were discovered via microarray analysis in the spinal cord of diabetic mice. Four of the lncRNAs (ENSMUST00000134111, NR_003513, ENSMUST00000150952, and AK047066) were verified by qPCR, and the results were in accordance with the sequencing results. Moreover, through the analysis of these differentially expressed genes, Du et al. detected 346 related lncRNA–mRNA pairs that participate in the process of NP.

On the basis of the increasing discovery of the functional properties of differentially expressed lncRNAs in NP, several studies have further discussed the functions and molecular mechanisms of certain lncRNAs acting on NP (Table 2). The lncRNA X-inactive specific transcript (XIST) is 1 of the lncRNAs that plays a key role in the regulation of X chromosome inactivation. Notably, several studies have proven that XIST is upregulated in NP animal models, including the CCI rat model, SCI rat model, and complete Freund's adjuvant (CFA) rat model. The

**Table 2** Functional characterization of the lncRNAs in NP

| LncRNA | Expression | Target genes | Related genes | Model | Region | Functions | Reference |
|---|---|---|---|---|---|---|---|
| XIST | Up | miR-150 | ZEB1 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [102] |
| | | miR-137 | TNFAIP1 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [103] |
| | | miR-154-5p | TLR5 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [104] |
| | | miR-494 | STAT3 | SCI rat model | Spinal cord | Apoptosis | [105] |
| | | miR-544 | STAT3 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [18] |
| | | miR-146a | Nav1.7 | CFA rat model | DRG | Neuroinflammation | [106] |
| MALAT1 | Up | miR-154-5p | AQP9 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [107] |
| | | miR-129-5p | BDNF | PNI mice model | Schwann cell | Proliferation and migration | [108] |
| | | miR-129-5p | HMGB1 | CCI rat model | Spinal cord, microglia | Neuroinflammation | [109] |
| | | miR-206 | ZEB2 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [110] |
| uc.48+ | Up | $P2X_7$ receptor | p-ERK1/2 | TN rat model | Trigeminal ganglia | Phosphorylation | [111] |
| | | | – | Diabetic rat model | DRG | Neuroinflammation | [112] |
| | | | p-ERK1/2 | Diabetic rat model | Superior cervical ganglia | Autonomic neuropathy | [113] |
| BC168687 | Up | $P2X_7$ receptor | – | Diabetic rat model | DRG | Neuroinflammation | [114] |
| | | TRPV1 | TNF-α, IL-1β, ERK, MAPK | Diabetic rat model | DRG | Neuroinflammation | [115] |
| | | $P2X_7$, TRPV1 receptor | – | Diabetic rat model | DRG | Neuronal excitability | [116] |
| NONRATT021972 | Up | $P2X_3$ receptor | ERK1/2, p-ERK | Diabetic rat model | DRG | Neuroinflammation | [117] |
| | | $P2X_7$ receptor | – | Diabetic rat model | Superior cervical ganglion, PC12 cell | Neuroinflammation | [118] |
| | | P2X7 receptor | – | Diabetic rat model | DRG | Neuroinflammation | [119] |
| BC088259 | Up | Vimentin | – | SNI rat model | Schwann cell | Migration | [120] |
| Linc00657 | Up | miR-136 | ZEB1 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [121] |
| CRNDE | Up | miR-136 | IL6R | CCI rat model | Spinal cord, microglial | Neuroinflammation | [122] |
| NEAT1 | Up | miR-381 | HMGB1 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [19] |
| uc.153 | Up | miR-182-5p | EphB1-NMDA receptors | CCI mice model | Spinal cord | Neuronal excitability | [123] |
| Linc00052 | Up | miR-448 | JAK1 | SNL rat model | Spinal cord, PC12 cell | Neuroinflammation | [124] |
| Linc00311, AK141205 | Up | STAT3 | CCL-2, COX-2, IL-1β, IL-6, and TNF-α | CCI rat model | Microglia | Neuroinflammation | [125] |
| SNHG5 | Up | miR-154-5p | CXCL13 | | DRG, microglia | | [126] |

**Table 2** (continued)

| LncRNA | Expression | Target genes | Related genes | Model | Region | Functions | Reference |
|---|---|---|---|---|---|---|---|
| | | | | CCI rat model | | Astrocyte inhibition, microglia activation | |
| H19 | Up | – | – | SNL rat model | DRG | Neuroinflammation | [127] |
| H19 | Up | – | – | SNL mice model | DRG, DRG cell | Neuronal excitability | [128] |
| PKIA-AS1 | Up | – | CDK6 | SNL rat model | Spinal cord | Neuroinflammation | [129] |
| BC088327 | Up | – | Heregulin-1β | PNI rat model | Sciatic nerve | Proliferation | [130] |
| MRAK009713 | Up | $P2X_3$ receptor | – | CCI rat model | DRG | Neuronal excitability | [131] |
| Kcna2 AS RNA | Up | Kcna2 mRNA | G9a | CCI/SNL mice model | DRG | Neuronal excitability | [132] |
| | | Kcna2 mRNA | – | CCI/SNL rat model | DRG | Neuronal excitability | [133] |
| DGCR5 | Down | miR-330-3p | PDCD4 | CCI rat model | Spinal cord, microglial | Neuroinflammation | [134] |
| TNXA-PS1 | Down | miR-24-3p/miR-152-3p | Dusp1 | SNI rat model | DRG | Migration | [135] |
| CCAT1 | Down | miR-155 | SGK3 | CCI rat model | DRG, spinal cord, hippocampus, anterior cingulate cortex, PC12 cell | Neuronal excitability | [136] |
| uc.217 | Down | – | – | SNI rat model | DRG | Neurite outgrowth | [137] |
| BC089918 | Down | – | – | SNI rat model | DRG | Nerve regeneration | [138] |

CCI = sciatic nerve chronic constriction injury; SCI = spinal cord injury; CFA = complete Freund's adjuvant; PNI = peripheral nerve injury; TN = trigeminal neuralgia; DRG = dorsal root ganglia; XIST = X-inactive specific transcript; ZEB1 = zinc finger E-box-binding homeobox 1; TNFAIP1 = tumor necrosis factor alpha-induced protein 1; TLR5 = toll-like receptor 5; STAT3 = signal transducer and activator of transcription 3; MALAT1 = metastasis-associated lung adenocarcinoma transcript 1; AQP9 = aquaporin 9; BDNF = brain-derived neurotrophic factor; HMGB1 = high mobility group protein B1; TRPV1 = transient receptor potential vanilloid type 1; IL = interleukin; TNF-α = tumor necrosis factor-α; ERK = extracellular regulated protein kinases; MAPK = mitogen-activated protein kinases; CRNDE = Colorectal Neoplasia Differentially Expressed; JAK1 = Janus kinase 1; CCL-2 = chemokine CC motif ligand 2; COX-2 = cyclooxygenase 2; SNHG5 = small nucleolar RNA host gene 5; CXCL13 = C-X-C motif chemokine 13; CDK6 = cyclin-dependent kinases 6; NF-κB = nuclear factor-κB; Dusp 1 = Dual-specificity phosphatase 1; CCAT1 = colon cancer–associated transcript-1; SGK3 = Serum and glucocorticoid–regulated protein kinase 3

silencing of XIST could reduce neuroinflammation and relieve pain-like behavior in NP [18, 102–106]. Several studies have indicated that lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) significantly increased in the spinal cord or Schwann cells. Reducing the expression of MALAT1 could improve pain-like behavior and repress the progression of inflammation, proliferation, and migration by regulating target genes [107–110]. The lncRNAs uc.48+ [111–113], BC168687 [114–116], and NONRATT021972 [117–119] were also upregulated in the NP animal models. They relieved hyperalgesia and decreased neuroinflammation by modulating the $P2X_3$ receptor or $P2X_7$ receptor. In addition to the lncRNAs reported above, some lncRNAs have also been reported to be associated with NP [19, 120–138]. For more detailed information, see Table 2.

## circRNAs and NP

The circRNAs were first reported in viroids in 1976, and they are closed circular RNA molecules without 3′ polyadenylated tails or terminal 5′ caps [139, 140]. Abundant circRNAs were found with the advancement of RNA sequencing analyses, beginning in approximately 2010. More than 10,000 circRNAs have been found in various fungi, plants, and animals [141]. At present, 4 kinds of circRNAs have been identified: intergenic circRNAs, exon–intron circRNAs

(EIciRNAs), and circRNAs from introns and exonic circRNAs (ecircRNAs) [142]. In addition, many circRNAs showed dynamic expression in various physiological and pathological scenarios, including cell apoptosis and cancer [143, 144]. Given that circRNAs have circular structures and are not influenced by RNA exonuclease, the expression of circRNAs could be more stable than the expression of linear RNAs [145–147]. The mechanism and function of circRNAs could not be fully identified; however, an increasing number of studies have revealed that circRNAs play a critical role in the diagnosis and treatment of different diseases.

Expression profiles of circRNAs were revealed in NP induced by CCI of the sciatic nerve and SNI [15, 148]. Cao et al. [149] used a circRNA microarray to detect the differential expression of circRNAs between CCI NP model rats and sham CCI rats. A total of 469 differentially expressed circRNAs could be found in the spinal dorsal horn between sham and CCI rats (fold change ≥ 2). In the CCI group, 106 of 469 circRNAs were statistically downregulated, and the other 363 were upregulated. The expression of 3 circRNAs (circRNA_003724, circRNA_008008, and circRNA_013779) was more than 10 times higher in the CCI group than in the sham group. The expression levels of 4 downregulated circRNAs (circRNA_011111, circRNA_007419, circRNA_007512, circRNA_010913) and 4 upregulated circRNAs (circRNA_008973, circRNA_013779, circRNA_008646, circRNA_35215) were validated by qPCR in the CCI group. Another study [15] used RNA sequencing analyses to predict the expression patterns of circRNAs between the SNI NP rat model and sham SNI rats. Compared with the sham group, Zou et al. [15] found that 188 circRNAs (120 downregulated and 68 upregulated) were abnormally expressed in the spinal cord of rats in the SNI group at 14 days after surgery. The expression of 2 selected circRNAs (circ 0004058 and circ 0005854) was verified by qPCR.

Currently, although few studies have revealed the functional roles of circRNAs in NP, several studies have reported the mechanism and function of circRNAs in the development and progression of NP (Table 3). Zhang and colleagues [20] found that the expression of circAnks1a was significantly upregulated in the spinal cord of SNL rats after 3, 7, 10, and 14 days compared with sham SNL rats. Notably, the pain-like behavior of SNL rats could be relieved through the downregulation of circAnks1a by siRNA. circAnks1a alleviated NP by regulating the vascular endothelial growth factor B (VEGFB) expression to decrease the excitability of the spinal cord in SNL rats. Pan and colleagues [149] demonstrated that the expression of the circRNA filamin A interacting protein 1-like (Filip1l) was significantly increased in spinal neurons of CCI mice and CFA-induced chronic inflammatory pain mice. The downregulation of circRNA Filip1l could alleviate the pain-like behavior in CFA mice by the injection of anti-Filip1l. The circRNA Filip1l regulated chronic pain by targeting ubiquitin protein ligase E3 component n-recognin 5 (Ubr5). Mao and colleagues [153] found that the circRNA ankyrin repeat and in-between Ring finger (IBR) domain containing 1 (Ankib1) was downregulated at 1, 4, 7, and 14 days after PNI in the sciatic nerve, which targeted cytochrome P450, family 26, subfamily B, polypeptide 1 (Cyp26b1) to regulate Schwann cell proliferation in the sciatic nerve. Zhou and colleagues [152] reported that, compared with sham PNI rats, circRNA-2837 was inhibited in the spinal cord of PNI rats and targeted LC3-II and p62 to regulate neuronal autophagy. Wang and colleagues [150] revealed that the expression of circHIPK3 was significantly upregulated in the DRG of NP-induced diabetic rats. In addition, the circHIPK3 regulated IL-1b, IL-6, IL-12, and tumor necrosis factor (TNF)-α to alleviate NP by inhibiting inflammation in diabetic NP rats. Cai and colleagues [151] demonstrated that ciRS-7 was significantly increased and that the degree of inflammation and autophagy was also upregulated in the spinal cord of CCI rats.

## Interactions Among lncRNAs, miRNAs, and mRNAs in NP

Recently, extensive evidence suggests that the lncRNA–miRNA–mRNA axis plays a critical role in the physiology and pathology of many diseases, including cancer, osteoarthritis, and cardiovascular diseases [98, 154, 155]. The potential mechanisms of lncRNA, miRNA, and mRNA interactions are as follows: 1) lncRNA acts as a competitive endogenous RNA (ceRNA) to sponge miRNA. lncRNAs have the effect of keeping miRNA away from mRNAs. These lncRNAs are called ceRNAs. They act as sponges for miRNAs, reducing the number of available miRNAs and helping to improve the translation of target mRNAs. For example, Cheng and his colleagues found that the lncRNAs CRNDE and MALAT1 may sponge miRNAs related to sepsis, participating in the regulation of sepsis modules [156]. Another study showed that the lncRNA TPTE pseudogene 1 (TPTEP1) could suppress the process of proliferation in lung cancer by sponging miR-328-5p [157]. 2) miRNA leads to the degradation of lncRNA. miRNAs can change the abundance of lncRNAs by reducing the stability of their target lncRNAs, thus affecting diverse cellular processes. For example, miR-145-5p was a target gene of lncRNA-RoR in human embryonic stem cells, whereas increasing the concentration of miR-145-5p reduced the activity of lncRNA-RoR [158]. 3) lncRNA combines with mRNA by competing with miRNA. lncRNAs can directly bind to complementary mRNAs at the miRNA–mRNA binding site region, thereby removing the regulation of miRNA on mRNA. For example, the tumor-related lncRNA noncoding Nras functional RNA (ncNRFR) decreases the function of let-7 by competing with let-7 for target mRNAs [159]. 4) lncRNA

**Table 3** Functional characterization of the circRNAs in NP

| circRNA | Expression | Target genes | Related genes | Model | Region | Functions | Reference |
|---|---|---|---|---|---|---|---|
| circ-Filip1l | Up | miRNA-1224 | Ago2, Ubr5 | CCI mice model | Spinal cord, astrocytes, and microglia | Neuroinflammation | [149] |
| circHIPK3 | Up | miR-124 | IL-1b, IL-6, IL-12, and TNF-α | Diabetic rat model | DRG, PC12 cell | Neuroinflammation | [150] |
| ciRS-7 | Up | miR-135a-5p | IL-6, IL-12, TNF-α, Iba1 and Beclin-1, p62, LC3-I, LC3-II | CCI rat model | Spinal cord | Neuroinflammation, autophagy | [151] |
| circRNA.2837 | Down | miR-34a | LC3-II, p62 | SNI rat model | Spinal cord, sciatic nerve | Neuronal autophagy | [152] |
| circ-Ankib1 | Down | miR-423-5p/485-5p/666-3p | DHX9, Cyp26b1 | Sciatic nerve crush rat model | Schwann cell | Proliferation | [153] |
| circAnks1a | Up | miR-324-3p | VEGFB, YBX1 | SNL rat model | Spinal cord | Central sensitization | [20] |

CCI = sciatic nerve chronic constriction injury; SNI = spared nerve injury; SNL = sciatic nerve ligation; DRG = dorsal root ganglia; Ago2 = Argonaute-2; Ubr5 = ubiquitin protein ligase E3 component n-recognin 5; IL = interleukin; TNF-α = tumor necrosis factor-α; Ankib1 = ankyrin repeat and in-between Ring finger (IBR) domain containing 1; DHX9 = DEx/H-box helicase 9; Cyp26b1 = cytochrome P450, family 26, subfamily B, polypeptide 1

generates miRNA. For example, it has been reported that lncRN-MD1 could generate miR-206 and miR-133, playing roles in muscle differentiation and dystrophy [160]. However, it has been reported that the reciprocity of ncRNAs is involved in the pathological process of NP, including neuroinflammation, cell migration, and cell apoptosis. The potential mechanism of lncRNA, miRNA, and mRNA acting on NP is that lncRNAs serve as ceRNAs, thereby sponging miRNAs and inhibiting their downstream target genes (Fig. 1).

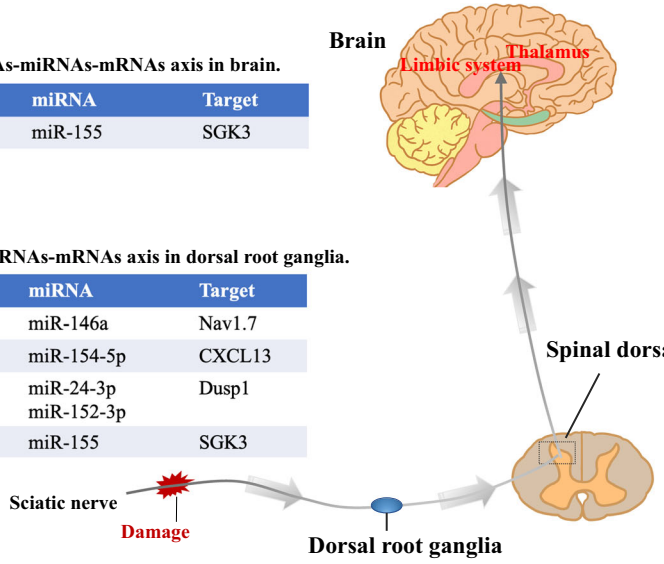
Several studies have proven that the lncRNA XIST was significantly upregulated in the CCI or CFA animal model, and XIST could induce the neuroinflammation of NP by regulating the target mRNAs as sponges of miR-150, miR-137, miR-154-5p, miR-544, and miR-146a [18, 102–104, 106]. Another study showed that the knockdown of XIST could relieve pain-like behavior and apoptosis in the spinal cord of SCI rats by competitively sponging miR-494, thereby negatively modulating the expression of AKT [105]. In addition, there were articles reporting that the lncRNA MALAT1 participated in the process of NP by sponging miRNA-154-5p, miR-129-5p, and miR-206. The downregulation of MALAT1 or its target mRNAs helps relieve pain and repress inflammation, proliferation, and migration [107–110]. Yao et al. demonstrated that the lncRNA TNXA-PS1 was significantly decreased in the DRG of SNI rats. Furthermore, they indicated that TNXA-PS1 could competitively bind with miR-24-3p/miR-152-3p, thereby modulating migration in the DRG by controlling the expression of Dusp1 [135]. Chen and colleagues [126] clarified that lncRNA SNHG5 could sponge miR-154-5p to modulate C-X-C motif chemokine 13 (CXCL13) in CCI rats and that the knockdown of SNHG5 could relieve pain and suppress the sensitization of astrocytes and microglia. Shen et al. and Zhang et al. [121, 122] found that lncRNA00657 and the lncRNA CRNDE were significantly increased in the CCI rat model, and they could regulate ZEB1 and interleukin 6 receptor (IL6R) by sponging miR-136. Based on the study of Xia et al. [19], the lncRNA NEAT1 was overexpressed in the CCI rat model. The NEAT1 modulated the expression of HMGB1 to relieve pain and decrease inflammation by sponging miR-381 in the spinal cord and microglia of CCI rats. Zhang and colleagues [123] found that the lncRNA uc.153 played regulatory roles in NP via competitive combination of miR-182-5p and then the regulation of EphB1-NMDA receptors. Wang et al. suggested that lnc00052 [124] could induce pain-like behavior and inflammation in the spinal cord of SNL rats by sponging miR-448 and modulating JAK1. Compared with sham CCI, the lncRNA DGCR5 was downregulated in the spinal cord of CCI rats. DGCR5 could negatively regulate the expression of miR-330-3p and suppress neuroinflammation and hyperalgesia by sponging miR-330-3p and modulating the downstream target PDCD4 [134]. Dou and colleagues [136] showed that the lncRNA CCAT1 was significantly decreased in the DRG, spinal cord, hippocampus, and anterior cingulate cortex of CCI rats. CCAT1 could inhibit pain-like behaviors by sponging miR-155 and then regulating the expression level of SGK3. The abovementioned results showed that lncRNAs could serve as miRNA sponges in the interactions among lncRNAs, miRNAs, and mRNAs in NP.

A. lncRNAs-miRNAs-mRNAs axis in brain.

| lncRNA | miRNA | Target |
|---|---|---|
| CCAT1 ↓ | miR-155 | SGK3 |

B. lncRNAs-miRNAs-mRNAs axis in dorsal root ganglia.

| lncRNA | miRNA | Target |
|---|---|---|
| XIST ↑ | miR-146a | Nav1.7 |
| SNHG5 ↑ | miR-154-5p | CXCL13 |
| TNXA-PS1 ↓ | miR-24-3p<br>miR-152-3p | Dusp1 |
| CCAT1 ↓ | miR-155 | SGK3 |




C. lncRNAs-miRNAs-mRNAs axis in spinal dorsal horn.

| lncRNA | miRNA | Target |
|---|---|---|
| XIST ↑ | miR-150 | ZEB1 |
| | miR-137 | TNFAIP1 |
| | miR-154-5p | TLR5 |
| | miR-494 | PTEN/AKT |
| | miR-544 | STAT3 |
| MALAT1 ↑ | miR-154-5p | AQP9 |
| | miR-129-5p | BDNF |
| | miR-129-5p | HMGB1 |
| | miR-206 | ZEB2 |
| Linc00657 ↑ | miR-136 | ZEB1 |
| CRNDE ↑ | miR-136 | IL6R |
| NEAT1 ↑ | miR-381 | HMGB1 |
| uc.153 ↑ | miR-182-5p | EphB1-NMDA |
| Linc00052 ↑ | miR-448 | JAK1 |
| DGCR5 ↓ | miR-330-3p | PDCD4 |
| CCAT1 ↓ | miR-155 | SGK3 |

**Fig. 1** lncRNA–miRNA–mRNA axis in NP. The noxious stimulus reaches the spinal dorsal horn via the afferent nerve fibers. Spinal dorsal horn is the center responsible for integrating and processing input information. The output from the spinal cord network is then sent to higher cortical centers. The thalamus and limbic system are important parts of the brain for NP expression. The roles of the lncRNA–miRNA–mRNAs axis in NP was reflected in the DRG, spinal dorsal horn, and brain regions. CCAT1 = colon cancer–associated transcript-1; SGK3 = serum and glucocorticoid–regulated protein kinase 3; XIST = X-inactive specific transcript; SNHG5 = small nucleolar RNA host gene 5; CXCL13 = C-X-C motif chemokine 13; Dusp 1 = Dual-specificity phosphatase 1; ZEB = zinc finger E-box-binding homeobox; TNFAIP1 = tumor necrosis factor alpha-induced protein 1; TLR5 = toll-like receptor 5; STAT3 = signal transducer and activator of transcription 3; AQP9 = aquaporin 9; BDNF = brain-derived neurotrophic factor; HMGB1 = high mobility group protein B1; IL6R = interleukin 6R, JAK1 = Janus kinase 1

## Interactions Among circRNAs, miRNAs, and mRNAs in NP

At present, many studies focus on the novel mechanism underlying the interactions among circRNAs, miRNAs, and mRNAs. Cross-talk was found between circRNAs and miRNAs, which regulated the relevant mRNA expression in physiologic processes and pathological mechanisms [161–163]. The interactions among circRNAs, miRNAs, and mRNAs could participate in the pathological mechanisms of NP, such as neuroinflammation [149, 150], neuronal excitability [20], cell proliferation [153], and neuronal autophagy [152] (Fig. 2). The relative interaction mechanisms among circRNAs, miRNAs, and mRNAs are debated; however, 2 kinds of mechanisms could be identified: 1) circRNAs sponging miRNAs. Song et al. found that circHMCU, as a sponger of the let-7 family, played a crucial role in the proliferation and metastasis of breast cancer [164]. Another study showed that the circRNA MAN2B2 was abnormally expressed in hepatocellular carcinoma tissues. The knockdown of the circRNA MAN2B2 could suppress the process of cell proliferation in the hepatocellular carcinoma cells by sponging miR-217 [165]. 2) miRNAs mediating circRNAs. Hansen and his colleagues found that miR-671 mediated the cleavage of the circRNA cerebellar degeneration-related protein 1 (CDR1) in the mouse brain [166].

The novel mechanism of "circRNAs sponging miRNAs" is frequent in the cross-talk among circRNAs, miRNAs, and mRNAs in NP. Compared with sham SNL, circAnks1a was overexpressed in the SNL model of NP. circAnks1a regulated the VEGFB expression to reduce the excitability of the spinal cord by sponging miR-324-3p in the spinal cord of SNL rats [20]. Based on the research of Mao et al. [153], their results showed that circ-Ankib1 was verified to sponge miR-423-5p, miR-485-5p, and miR-666-3p and then regulate Schwann cell proliferation by targeting the Cyp26b1 protein in PNI. As shown in the research of Zhou et al. [152], circRNA-2837 could sponge the miR-34 family (miR-34a, miR-34b, and miR-34c) to regulate LC3-II and p62 in SNI rats and then protect neurons by decreasing neuronal autophagy. Wang and colleagues [150] found that circHIPK3 could alleviate pain by sponging miR-124, which induced inflammation by regulating IL-1b, IL-6, IL-12, and TNF-α in diabetic NP rats. Cai and colleagues [151] showed that ciRS-7 was involved in regulating inflammation and autophagy in NP progression by sponging miR-135-5p. These results demonstrated the novel mechanism of "circRNAs sponging miRNAs" in NP.

Few studies have revealed the novel mechanism of "miRNAs mediating circRNAs" in the cross-talk among

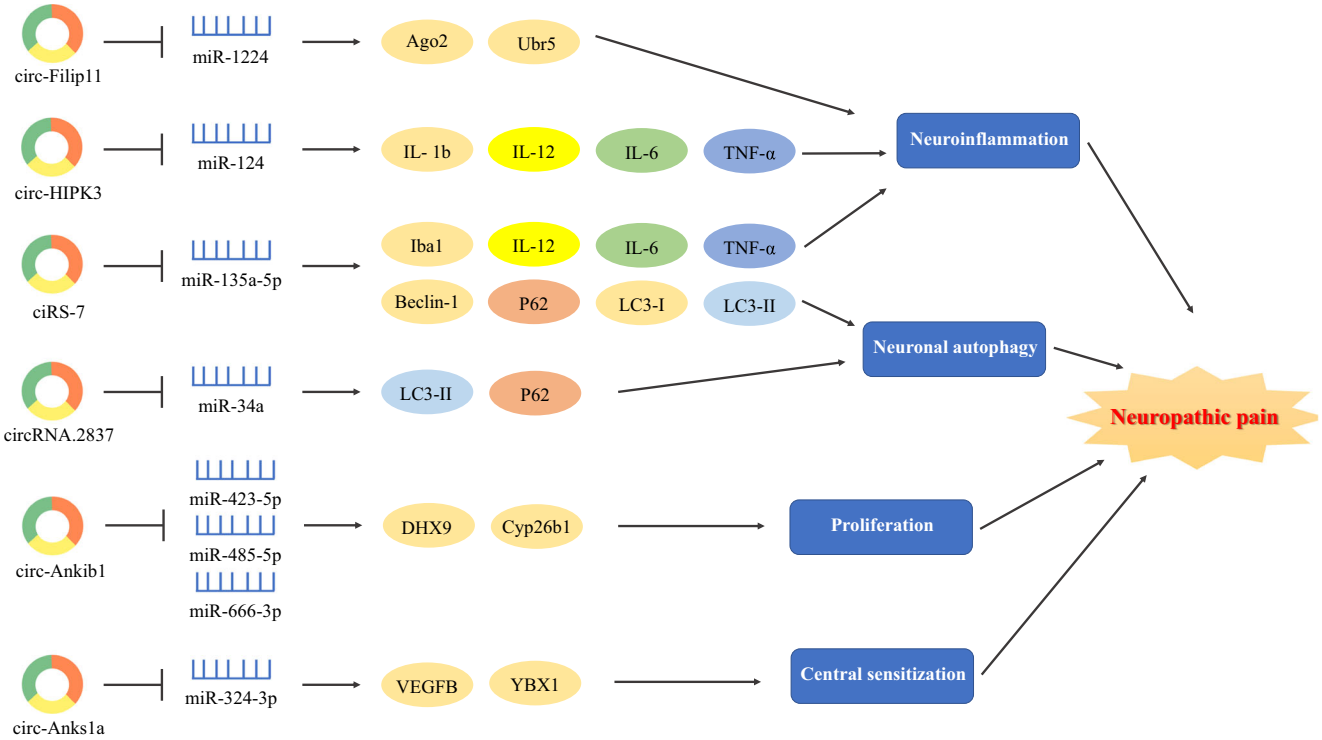



**Fig. 2** circRNA–miRNA–mRNA axis in NP. circRNAs could regulate the target genes by sponging miRNAs, leading to the emergence and development of NP. Ago2 = Argonaute-2; Ubr5 = ubiquitin protein ligase E3 component n-recognin 5; IL = interleukin; TNF-α = tumor necrosis factor-α; Ankib1 = ankyrin repeat and in-between Ring finger (IBR) domain containing 1; DHX9 = DEx/H-box helicase 9; Cyp26b1 = cytochrome P450, family 26, subfamily B, polypeptide 1

circRNAs, miRNAs, and mRNAs in NP. Based on the research of Pan et al. [149], miR-1224 expression was downregulated in the spinal cord at 1, 3, and 7 days after CFA-induced chronic inflammatory pain, and the expression of spinal circRNA-Filip1l increased because of the reduction of miR-1224 expression through the binding and splicing of precursor of circRNA-Filip1l in an Argonaute-2-dependent manner. The knockdown of miR-1224 resulted in thermal hyperalgesia and mechanical allodynia in mice. They found that the ubiquitin protein ligase E3 component n-recognin 5 (Ubr5) was a target gene of circRNA-Filip1l and played vital roles in the modulation of nociception. Pan and colleagues [149] revealed that miR-1224 could mediate circRNA-Filip1l expression by regulating the Ubr5 in the spinal cord of CFA rats. Their results proved the novel mechanism of "miRNAs mediating circRNAs" for the interactions among circRNAs, miRNAs, and mRNAs in chronic pain.

## Clinical Implications

Recently, it has been widely reported that aberrant expression of ncRNAs exists after NP injury, and these differentially expressed ncRNAs are considered to be potential biomarkers for the diagnosis, assessment, treatment, prediction, and prognosis of NP. For example, Heyn et al. showed that miR-124a and miR-155 were significantly increased in patients with NP compared with healthy volunteers. However, the aberrant expression of these miRNAs repressed the expression of sirtuin1 (SIRT1), a direct target gene of miR-124a and miR-155, resulting in the overexpression of anti-inflammatory differentiation of regulatory T cells, thereby limiting the development of inflammation and relieving the pain [167]. Another study demonstrated that the level of the lncRNA NONRATT021972 was upregulated in the blood of patients with diabetic neuropathic pain, which was correlated with TNF-α pathways. Furthermore, in animal experiments, they further demonstrated that lncRNA NONRATT021972 siRNA could suppress inflammation and alleviate NP by decreasing TNF-α [168]. All these studies indicate that ncRNAs may act as potential biomarkers for clinical utility in patients with NP. However, because most of the existing studies are focused on animal NP models, these data are difficult to apply to humans. Therefore, further studies need to explore more clinical trials to provide more validated evidence that ncRNAs can be used in the diagnosis, treatment, and prognosis of NP.

## Conclusion and Future Prospects

Recently, studies on ncRNAs in NP have become increasingly extensive. The role of miRNAs in NP has been studied the

most, but its mechanism in NP is still unclear because of its wide range of target genes and different signaling pathways. Considering the improvement of high-throughput sequencing technologies, such as microarray and RNA sequencing, a large number of lncRNAs and circRNAs have been discovered, thereby elucidating transcriptome complexity and demonstrating the dysregulation of the expression of many lncRNAs and circRNAs in NP. Therefore, these findings suggest the importance of explorations of the potential use of ncRNAs as biomarkers and potential therapeutic targets for NP. However, the annotated ncRNAs that we have discussed may be just the tip of the iceberg. More broadly, future research is also needed to determine more valuable functions of ncRNAs in the process of NP.

lncRNAs and circRNAs have been successively added to the miRNA network and can be used as "miRNA sponges" to regulate miRNA expression in NP. However, because the study was limited to the obtained clinical specimens, it was difficult to further explore the network mechanism of the lncRNA/circRNA–miRNA–mRNA axis. In future investigations, subsequent in-depth studies are required to verify clinical diagnosis and treatment protocols and to utilize the lncRNA/circRNA–miRNA–mRNA axis as a treatment target in NP.

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## Compliance with Ethical Standards

**Competing Interests** The authors declare that they have no competing interests.

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