

Differential Expression of Long Non-Coding RNAs and Their Role in Rodent Neuropathic Pain Models

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Abstract: Neuropathic pain, which is accompanied by an unpleasant sensation, affects the patient's quality of life severely. Considering the complexity of the neuropathic pain, there are huge unmet medical needs for it while current effective therapeutics remain far from satisfactory. Accordingly, exploration of mechanisms of neuropathic pain could provide new therapeutic insights. While numerous researches have pointed out the contribution of sensory neuron-immune cell interactions, other mechanisms of action, such as long non-coding RNAs (lncRNAs), also could contribute to the neuropathic pain observed in vivo. LncRNAs have more than 200 nucleotides and were originally considered as transcriptional byproducts. However, recent studies have suggested that lncRNAs played a significant role in gene regulation and disease pathogenesis. A substantial number of long non-coding RNAs were expressed differentially in neuropathic pain models. Besides, therapies targeting specific lncRNAs can significantly ameliorate the development of neuropathic pain, which reveals the contribution of lncRNAs in the generation and maintenance of neuropathic pain and provides a new therapeutic strategy. The primary purpose of this review is to introduce recent studies of lncRNAs on different neuropathic pain models.

Keywords: neuropathic pain, long non-coding RNAs, pain model, treatment, microarray analysis

Introduction

Overview of Neuropathic Pain

Pain is a common disease in clinical practice, which has important implications for the human body. Pain perception has evolved as a warning role to respond to organismic danger and tissue damage in a timely manner, then it presents a protective effect by generating related danger signals.¹ Patients are deeply troubled by the continuous generation of pain signals and the dysfunction of the nervous system. As generally known, neuropathic Pain is a common chronic pain in clinical practice. It is generally caused by the dysfunction of somatosensory neurons in the central or peripheral nervous systems.² Recently, neuropathic pain was redefined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" by the International Association for the Study of Pain (IASP).³ The primary diseases include neurological damage caused by cancer, diabetes, infection, autoimmune diseases, chemotherapy, or trauma.⁴ These conditions usually lead to chronic pain syndrome, manifesting as spontaneous pain, hyperalgesia and allodynia. In addition, chronic pain has been

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shown to cause sleep disturbances, mental illnesses and difficulty in concentrating.⁵ Nearly 8% of the world's people suffer from chronic pain, which seriously affects the quality of life.⁶

The primary causes for those symptoms of chronic pain include alteration of ion channels (such as calcium and sodium channels) in neurons,^{7,8} activation of immune cells (like microglia, macrophage and CD4+T cell et al) and systemic inflammatory imbalance.^{1,9,10} These results ultimately lead to imbalance between the ascending pain pathways and the descending inhibitory pathway. In sensory transduction, dorsal root ganglion (DRG) is the gathering place of the somatosensory primary afferent neuron cell body and it is of vital importance in the signal transmission between peripheral stimuli and central sensory system.¹¹ Admittedly, the pathogenesis of neuropathic pain is complicated. In the beginning, it seems that few neurons were damaged, which led to abnormal electrical activity, synaptic changes and continuous inflammation.^{12,13} Further studies have found that the production of chronic pain includes the abnormal production of pro-inflammatory mediators and the interaction between neurons and immune cells as well.^{14,15} It contains a complex network system composed of microglia and macrophages.^{15,16} For example, colony-stimulating factor 1 (CSF1) induces microglial proliferation and aggravates the pain dramatically.⁹ Reduction of macrophages in DRG can relieve mechanical and thermal hyperalgesia.¹⁷ Besides, Some new studies show that receptors such as melanocortin 4 receptor (MC4R) and Toll-like receptor 4 (TLR4) are also helpful.^{18,19} Here, we briefly reviewed recent studies of lncRNAs in neuropathic pain, focusing on different rodent neuropathic pain models.

Biological Functions of Long Non-Coding RNAs

The human transcriptome has pointed that only 1–2% of the human genome is used to encode proteins, and the remaining 98% is non-coding RNA. lncRNAs is one of the non-coding RNA without protein-coding function. However, an important progression has been the emergence of lncRNAs as key post-transcriptional regulators.²⁰ Crucial roles for lncRNAs have been identified in conditions such as cardiovascular diseases, various cancers, autoimmune disorders, kidney and liver system, etc.^{21–23} Subsequent studies have shown that lncRNAs play an essential role in gene expression by co-transcriptional regulation, post-transcriptional bridging proteins and

chromatin, pairing with other RNA and chromosomal modification,^{24,25} especially in the development, proliferation, differentiation, migration and invasion of tumors cells.²⁶ What's more, some lncRNAs could play a role in an indirect way, which interacts with microRNAs (miRNAs) and proteins to regulate signal transduction pathways downstream, affecting the development of various diseases.^{27,28}

Bioinformatic analysis and silico inference methods reveal potential interactions between lncRNAs-miRNAs and lncRNAs-RNA binding protein, which have attracted intense interest. miRNAs, small non-coding RNAs, play an important role in the post-transcriptional regulation.²⁷ The possible mechanisms for lncRNAs to regulate miRNA are as follows: (1) lncRNAs indirectly inhibits negative regulation of miRNA by competitively binding to the 3'-UTR of target mRNA.²⁹ (2) lncRNAs could act as a competitive endogenous RNA to play the "molecular sponge" and inhibit the expression of miRNA.^{30,31} (3) lncRNAs is a potential pri-miRNA, which indirectly regulates the expression of target genes.³² RNA-Protein interactions are key aspects in many biological processes.²⁸ The primary concern of the present studies is shifting the attention from RNAs (like tRNAs, rRNAs) involved in translation and regulation towards lncRNAs.²⁰ The Encyclopedia of DNA Elements shows that the correspondence between lncRNAs and RBP is not one-to-one. lncRNAs can interact with multiple RBP and generate biological efficacy via regulating expression of genes or preventing association with DNA.³³ The association between them could be with potential therapeutic implications. While interactions of lncRNAs are more complex than previously thought, it still caused considerable concern and interest. It has been proven that lncRNAs plays an imperative role in tumors and participates in the generation and development of many diseases. In the meantime, a large amount of recent evidence shows that lncRNAs is also essential in neuropathic pain.³⁴

The Profiles of Differentially Expressed lncRNAs in Neuropathic Pain

In recent years, with the rapid improvement of sequencing technology, many studies have conducted more in-depth research on neuropathic pain from the perspective of genes. Stacks of differentially expressed genes were found in the dorsal horn of the spinal cord, DRG and other regions in neuropathic pain models.³⁵ Among them,

it would have indicated that long-chain non-coding RNAs play a fundamental role in disease regulation. Therefore, the lncRNAs will become crucial targets for the treatment of neuropathic pain.^{36,37}

Gene sequencing technology was being used in the rat neuropathic pain model to find many differentially expressed genes in the spinal cord and DRG. Therefore, bioinformatics analysis technology can be an ideal method to perform enrichment analysis and construct interactive network, revealing the molecular mechanism of lncRNAs in nerve damage and repair process.³⁶ lncRNAs still, in turn, regulate neurite outgrowth of DRG neuron.³⁶ Hu et al identified the differentially expressed lncRNAs in the spared nerve injury (SNL) model and found 1259 down-regulated and 2473 up-regulated lncRNAs in SNL rats. Among them, lncRNAs PKIA-AS1, small nucleolar RNA host gene 4(SNHG4), SH3 and cysteine-rich containing protein 3(STAC3) and CIRBP-AS1 were significantly up-regulated.³⁸ Besides, more than 800 differentially expressed genes have been discovered in the chronic constriction injury model.³⁹ A variety of differentially expressed genes were also detected in the neuropathic pain model of mice^{42–44} (Table 1). These studies provide the premise for studying the genetic level of neuropathic pain.

Major Neuropathic Pain Models

Promising new models for chronic pain provided a good base for further in-depth study of mechanisms. Photochemical and excitotoxic spinal cord injury are main central pain models. But the peripheral models seem to be more popular, which include chronic constriction injury (CCI), SNL, diabetic neuropathic pain (DNP), sciatic nerve injury (SCI) models and so on. In those studies, mechanical and thermal thresholds are important indicators to evaluate the hyperalgesia; and the content of inflammatory mediators usually reflects the degree of neuroinflammation. Nowadays, mature model of peripheral neuropathic pain has been established and major animal models are shown in Figure 1.⁴⁸

Latest Research Advances of lncRNAs in Neuropathic Pain Models

Based on the numerous researches on neuropathic pain-related lncRNAs, a large number of studies have found that lncRNAs are highly correlated with neuropathic pain, which provides a new target for its treatment.

SNL Model

There seems many lncRNAs expressed differentially in the SNL model (Table 2). Interaction between the lncRNAs and proteins is important. Firstly, Zhao et al discovered that the voltage-dependent potassium channel-related lncRNAs, KCNA2 antisense RNA, could regulate the excitability of DRG neurons by acting on zinc finger protein in rat, affecting the development and maintenance of neuropathic pain.⁵¹ The expression of lncRNA H19 in the DRG increased after SNL, and it is mainly up-regulated in Schwann cells—a non-primary sensory neuron, which likely be closely related to neuropathic pain.⁵² Recent studies have found that lncRNA embryonic stem cell expression 1 (Incenc1) is significantly upregulated in the DRG. Lncenc1 could bind to the RNA binding protein (RBP) enhancer of Zeste homologous protein 2 (EZH2), affecting the activation of microglia and the occurrence of neuropathic pain.⁵³ Hu et al performed array analysis on the spinal cord and found that lncRNA PKIA-AS1 is highly expressed in SNL rat model. It has proved that PKIA-AS1 can mediate neuropathic pain by regulating the expression and function of CDK6 in experiments. It seems that most of lncRNAs may interact with receptor indirectly in SNL model.

Besides, lncRNAs directly affects neuropathic pain as well as interacts with miRNAs' downstream. Linc00052 is significantly expressing in the spinal cord of SNL rats. The knockout of Linc00052 can inhibit the neuroinflammatory process through the miR-448-JAK1 axis, alleviating the development of neuropathic pain.⁵⁴ Studies have found that lncRNA p21 has been confirmed in vivo and in vitro experiments that it may act on miR-181b/Tnfrsf1 to activate the downstream AKT/CREB axis, regulating cell apoptosis and inflammatory factor secretion, then affecting neuropathic pain.⁵⁵ The small nucleolar RNA host gene (SNHG) family not only involves in the proliferation, metastasis and prognosis of tumors cells, but also affects the progression of neuropathic pain. LncRNA SNHG1 mainly induces pain by directly regulating the level of CDK4 in the spinal cord of SNL rats.⁵⁶ SNHG4 regulates miR-423-5p negatively, which promotes neuro-inflammation and affects the progression of neuropathic pain.⁵⁷ In addition, a significant up-regulation of SNHG5 has been revealed in the mouse SNL model. After knocking out the SNHG5 gene, the mechanical threshold and thermal threshold were significantly increasing. At the same time, the studies suggested that the activation of microglia could

Table 1 The Number of Differentially Expressed lncRNAs by Using Sequencing Technology in Multiple Models

Model	Method	Total DE lncRNAs	Up-Regulation	Down-Regulation	Tissue	Species	Ref.
CCI	Microarray analysis	876	339	537	L3-L5 spinal cord	Rat	[39]
SNi	Microarray analysis	105	81	24	L4-L6 DRGs	Rat	[36]
SNi	Microarray analysis	lncRNAs change over time.	/	/	L4-L5 spinal cord	Rat	[40]
SNi	Microarray analysis	112	/	/	L4-L6 DRGs	Rat	[41]
SNL	Microarray analysis	511	366	145	L5 spinal cord	Mice	[42]
SNi	Microarray analysis	1200	/	/	L4-L5 spinal cord	Mice	[43]
SNi	Microarray analysis	144	15	129	L4-L5spinal cord	Rat	[44]
SNL	Microarray analysis	1597	/	/	Bilateral L4 DRGs	Mice	[45]
SNL	Microarray analysis	3732	2473	1259	L5 spinal cord	Rat	[38]
DNP	High throughput sequencing	9	1	8	L4-L5 spinal cord	Mice	[46]
PIPn	High throughput sequencing	412	145	267	L4-L6 spinal cord dorsal horn	Rat	[47]

Note: "/" Indicates no mention in the article.

Abbreviations: CCI, chronic constriction injury; SNi, spared nerve injury; SNL, spinal nerve ligation; DNP, diabetic neuropathic pain; PIPn, paclitaxel-induced peripheral neuropathy.

be inhibited by regulating the miR-154-5p/CXCL13 axis, then neuropathic pain is reduced as well.⁵⁸ Such upregulation or downregulation of miRNA was highly correlated with the expression level of lncRNAs in the SNL model. As aforementioned, lncRNAs usually act as a “molecular sponge” to regulate neuroinflammation by lncRNAs–miRNAs axis. The result proven herein, affirms the indispensable role played by miRNA in development of neuropathic pain. As a result, lncRNAs is a new target for the treatment of neuroinflammatory neuropathic pain.³⁸

CCI Model

A large number of differentially expressed lncRNAs genes related to neuropathic pain were found in the spinal cord and DRG in CCI models (Table 3). Many studies have suggested that lncRNA X–inactive specific transcript (XIST) is significantly up-regulated in the spinal cord tissue and microglia of the CCI model, and it plays a significant role by regulating downstream molecules. For one thing, the development of neuropathic pain can be affected by acting on downstream miR-154-5p, which directs the expression of TLR5.⁵⁹ For another, lncRNA XIST was also reported that it could increase the expression of STAT3 (Signal transducer and activator of transcription 3) by regulating downstream miR-544, which then causes pain aggravation.⁶⁰ Besides, lncRNA XIST can not only negatively regulate miR-150 and zinc-finger E-box-binding (ZEB),⁶¹ but also act on miR-137 to enhance the expression of TNFAIP1, which can promote inflammation and aggravate the development of neuropathic pain.⁶² It demonstrates that lncRNA XIST plays an essential role in neuropathic pain. The targeted miRNAs of lncRNAs could be predicted by bioinformatics analysis technology, and the interrelations were followed up with animal experiments, which is helpful for the prediction of therapeutic targets. lncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is one of the diagnostic markers in many diseases.^{63,64} Research indicated that the expression of lncRNA MALAT1 was significantly up-regulated in the spinal cord and microglia of the CCI model, and it is considered to be a prominent target for pain regulation. Neuropathic pain could be regulated by changing the expression of miR-154-5p and AQP9 by lncRNA MALAT1.⁶⁵ lncRNA MALAT1 also interacts with downstream miR-129-5p to regulate the expression of HMGB1 (High-mobility group box 1), which can promote hyperalgesia.⁶⁶ In addition, deletion of MALAT1 gene can alleviate the development of

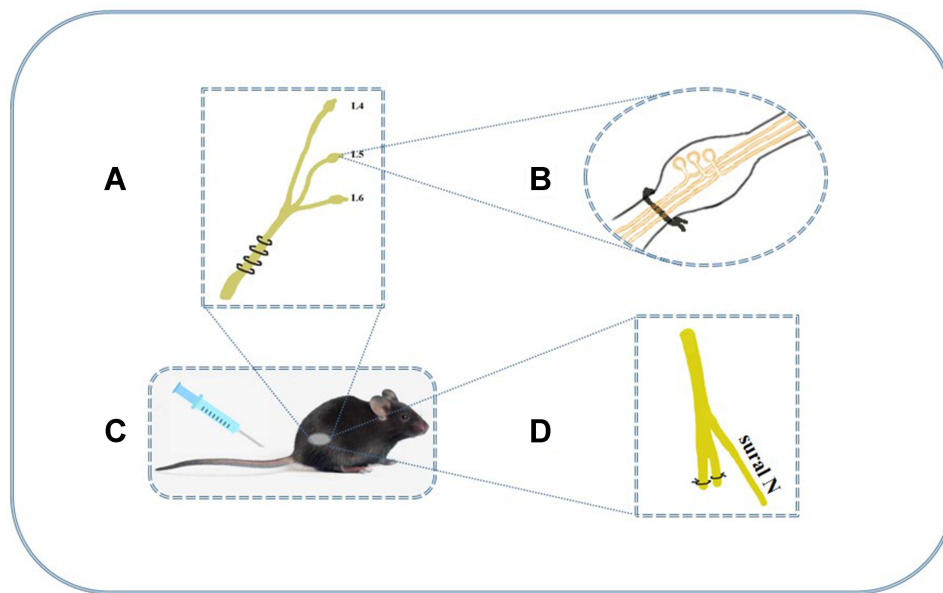


Figure 1 The major animal models of neuropathic pain. **(A)** The CCI model loosely ties the unilateral sciatic nerve below the mid-femur region with four chromic gut ligatures. It shows behavioral signs of spontaneous pain and hyperalgesia (thermal and tactile allodynia) and duration of pain signs persist over 2 months. **(B)** L5 and L6 spinal nerves of SNL model are tied unilaterally and closely at the distal side of dorsal root ganglia. It could indicate allodynia and hyperalgesia and last for at least 4 months. **(C)** DNP model was established by a single i.p. injection of streptozocin (STZ) and it induces thermal and mechanical hyperalgesia for 2–3 weeks.⁴⁹ **(D)** In SNI model, the common peroneal and tibial nerves was ligated and axotomized, but sural nerve remained intact. Paw withdrawal threshold after SNI is significantly lower than sham group and hyperpathia lasts for at least 1 month.⁵⁰

neuroinflammation by inhibiting expression of COX-2, IL-1 β and IL-6, while promoting up-regulation of miR-206 and inhibiting overexpression of ZEB2, which can improve the progression of neuropathic pain.⁶⁷ lncRNA XIST exists in a variety of biological processes as a ceRNA regulator network of miRNA-mRNA,⁶⁸ and it could potentially be involved in the therapy of neuropathic pain. As can be observed, the pain networks are highly complex and interconnected. For example, the expression of HMGB1 gene can be affected by lncRNA FIRRE and NEAT1 at the same time. Besides, other significantly differentially expressed lncRNAs and the downstream pathway in the CCI model provide new ideas and targets for its treatment.

DNP Model

The dominating manifestation of DNP model, common complications of type 2 diabetes, is accompanied by a burning sensation, acupuncture sensation and other abnormal sensations.^{81,82} The pathogenesis of diabetic neuropathic pain is complicated.⁸² Most recently, lncRNAs have attracted attention due to the continuous research on the mechanism of diabetic peripheral nerve pain. Related differentially expressed lncRNAs genes were parading in the DNP rat model (Table 4). Liu et al showed that inhibition of lncRNA BC168687 could reverse the threshold of

mechanical pain and thermal pain in DNP rats. It mainly interferes with the expression of TRPV1 in DRG and inhibits phosphorylation (P)-ERK and p-p38 signaling pathways at the same time,⁸³ They also found that lncRNA BC168687 acts on the P2X7 receptor in DRG, which relieves neuropathic pain by inhibiting its expression.⁸⁴ In addition, lncRNA NONRATT021972 is a gene that plays a pivotal role in DNP. After its expression was inhibited, in the DNP model, results showed that it could interact with the P2X3 and P2X7 receptors in DRG to alleviate the development of peripheral pain complications in diabetes.^{85,86} Increased expression of lncRNA uc.48+ was also demonstrated in DNP rat DRG and serum of diabetic patients, which can up-regulate the P2X3 receptor of DRG to regulate the excitability of neurons to affect the development of pain.⁸⁷ Besides, Xiong et al found that lncRNA uc.48+ could promote the release of calcitonin gene-related peptide (CGRP) in the spinal cord. When the expression of lncRNA uc.48+ is down-regulated, it can inhibit the phosphorylation of downstream p38 and ERK1/2, which will reduce the release of IL-1 β and TNF- α as well as alleviate hyperalgesia in DNP rats.⁸⁸ It is known that diabetic neuropathy is one of the diabetic complications and the patients are concomitant with maintaining a low quality of life. Now this illustrates

Table 2 Differential Expression of lncRNAs in SNL Model

Model	Name of lncRNA	Location of the Gene	Expression and Significance	Pathway/ Receptor	Biological Function	Tissue	Species	Gender	Ref.
SNL	H19	Chromosome 1 1q41	↑ *	STAT3/ TRPA1?	Activating inflammatory processes	Schwann cells/L5 DRG	Rat	Male	[52]
SNL	KCNA2	Chromosome 2 2q34	↓ **	MZF1	Regulation of Kcna2 channel expression and neuronal excitability	L4-L5 DRGs	Rat	-	[51]
SNL	Linc00052	/	↑ *	miR-448/ JAK1 axis	Regulating the behaviors of neuropathic pain and processes of neuroinflammation	L4-L6 dorsal spinal cord	Rat	Male	[54]
SNL	Lncenc1	Chromosome13 13 DI; 13	↑ **	RBP/EZH2 axis	The activation of microglia and production of inflammatory cytokines	L4-L6 DRGs and microglia	Mice	Male	[53]
SNL	P21	/	↑ **	MiR181b/ AKT/CREB axis	Promoting apoptosis and inflammatory factors secretion	L4-L6 dorsal spinal cords and microglia	Rat	Male	[55]
SNL	PKIA-AS1	/	↑ *	CKD6	Directly regulating the expression and function of CDK6 to maintain neuroinflammation and neuropathic pain	L5 spinal cord	Rat	Male	[38]
SNL	SNHG1	/	↑ *	CKD4	Influencing the development of NP by regulating neuroinflammation	L5 spinal cord	Rat	Male	[56]
SNL	SNHG4	Chromosome 18 18p11	↑ *	miR-423-5p	Regulating behaviors of neuropathic pain and neuroinflammation	L4-L6 dorsal spinal cord	Rat	Male	[57]
SNL	SNHG5	Chromosome 9 9; 9 E3.1	↑ **	miR-154-5p/ CXCL13 Axis	SNHG5 knockdown alleviated neuropathic pain and inhibited the activation of astrocytes and microglia	L5 DRG	Mice	Male	[58]

Notes: “?” Means possible pathway or receptor but has no studies in this article. “/” means no related location of genes were found in specific genera but it does not means absent. “-” indicates no mention in the article; * means P < 0.05, ** means P < 0.01.

Abbreviations: KCNA2-AS, KCNA2 antisense RNA; Lncenc1, lncRNA embryonic stem cells expressed 1; MZF1, myeloid zinc finger protein 1; SNHG, small nucleolar RNA host gene; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunits; CDK, cyclin dependent kinase; CXCL13, C-X-C motif chemokine ligand 13.

Table 3 Differential Expression of lncRNAs in CCI Model

Model	Name of lncRNAs	Location of the Gene	Expression and Significance	Pathway/ Receptor	Biological Function	Tissue	Species	Gender	Ref
CCI	XIST	Chromosome X	↑ **	miR-154-5p/ TLR5 axis	XIST can inhibit development of neuropathic pain	L4-L6 dorsal spinal cord	Rat	Female	[59]
CCI	XIST	Chromosome X	↑ **	miR-544/ STAT3 axis	Knockdown of XIST can relieve pain hyperalgesia and suppress expression of inflammatory cytokines	L4-L6 dorsal spinal cord	Rat	Female	[60]
CCI	XIST	Chromosome X	↑ *	miR-150/ZEB1 axis	Inhibition of XIST can inhibit neuropathic pain behaviors and alleviate neuroinflammation	L4-L6 dorsal spinal cord	Rat	Female	[61]
CCI	XIST	Chromosome X	↑ **	miR-137/ TNFAIP1 axis	XIST silencing relieve hyperpathia by regulating the expression of miR-137 and TNFAIP1	L4-L6 dorsal spinal cord	Rat	Female	[62]
CCI	MALAT1	/	↑ ***	miR-154-5p/ AQP9 axis	MALAT1 will promote neuropathic pain progression	Spinal cord and microglia	Rat	Female	[65]
CCI	MALAT1	/	↑ **	miR-129-5p/ HMGB1 axis	MALAT1 increase the development of neuropathic pain and neuroinflammation	L4-L6 dorsal spinal cord	Rat	Female	[66]
CCI	MALAT1		↑ *	miR-206/ZEB2 axis	Loss of MALAT1 can relieve pain behaviors and depress the neuroinflammation	L4-L6 dorsal spinal cord	Rat	Female	[67]
CCI	CRNDE	Chromosome19 19p11	↑ ***	miR-136/IL6R axis	Overexpression of CRNDE enhanced neuropathic pain behaviors and neuroinflammation	L4-L6 dorsal spinal cord	Rat	-	[69]

(Continued)

Table 3 (Continued).

Model	Name of lncRNAs	Location of the Gene	Expression and Significance	Pathway/ Receptor	Biological Function	Tissue	Species	Gender	Ref
CCI	DGCR5	/	↓ *	miR-330-3p/ PDCD4 axis	DGCR5 overexpression can alleviate neuropathic pain development	L4-L6 dorsal spinal cord	Rat	-	[70]
CCI	FIRRE	Chromosome X X; X A5	↑ *	HMGB1	LncRNA FIRRE downregulation inhibits the secretion of microglial cells-rived inflammatory cytokines	L4-L6 spinal cord	Mice	Female	[71]
CCI	Gas5	Chromosome 13 13q22	↓ *	miR-452-5p/ CELF2 axis	GAS5 overexpression will mitigate mechanical allodynia and thermal hyperalgesia	Spinal cord and microglia	Rat	Female	[72]
CCI	LINC00657	/	↑ *	miR-136/ZEB1 axis	Knockdown of LINC00657 will inhibit the neuroinflammation and alleviate hyperalgesia	L4-L6 dorsal spinal cord	Rat	Female	[73]
CCI	NEAT1	/	↑ *	miR-381/ HMGB1 axis	Knockdown of NEAT1 can repress neuropathic pain behaviors and inhibiting expression of IL-6, IL-1 β , and TNF- α	L4-L6 dorsal spinal cord	Rat	Female	[74]
CCI	DLEU1	/	↑ *	miR-133a-3p/ SRPK1 axis	DLEU1 knockdown reduces the neuroinflammation and inhibited neuropathic pain behaviors	Dorsal spinal cord	Rat	Female	[75]
CCI	H19	Chromosome 1 1q41	↑ **	miR-196a-5p/ CDK5 axis	Overexpression of H19 can alleviate hyperalgesia and upregulate inflammatory factors and GFAP levels, and reduced expression of 5-HT2A and GABAB2	L4-L5 dorsal spinal cord	Rat	-	[76]
CCI	MRAK009713	/	↑ **	P2X3 receptor	Highly expressed MRAK009713 markedly increased pain behaviors and expression of P2X3	DRG	Rat	Male	[77]
CCI	SNHG16	/	↑ ***	miR-124-3p and miR-141-3p/JAG1 axis	SNHG16 could increase the mechanical allodynia and thermal hyperalgesia and mRNA expression of inflammatory factors	Dorsal spinal cord	Rat	Female	[78]
CCI	uc.153	/	↑ ***	miR-182-5p/ EphB1-NMDA axis	uc.153 will promote pain behaviors and neuronal sensitization	L4-L5 dorsal spinal cord	Mice	Male	[79]

CCI	CRNDE	Chromosome 19 19p11	↑ ***	miR-146a-5p/ WNT5A	Silencing of CRNDE relieved mechanical allodynia, thermal hyperalgesia, and neuroinflammation	Dorsal spinal cord	Rat	Male	[80]
CCI	MEG3	/	↑ ***	miR-130a-5p/ CXCL12/ CXCR4	Up-regulating MEG3 aggravated NP, enhanced inflammatory cytokines expression and release.	L4-L6 dorsal spinal cord	Rat	Female	[80]
CCI	PCAT19	/	↑ ***	miR-182-5p/ JMJD1A	Mechanical pain and thermal hyperalgesia as well as neuroinflammation can be reduced by knocking down PCAT19	L4-L6 dorsal spinal cord	Rat	Male	[80]

Notes: “/” Means no related location of genes were found in specific genera but it does not means absent. “-” indicates no mention in the article; * means P < 0.05, ** means P < 0.01, and *** means P < 0.001.

Abbreviations: DGC5, DiGeorge syndrome critical region gene 5; NEAT1, Nuclear paraspeckle assembly transcript1; XIST, X inactivation-specific transcript; DLEU1, deleted in lymphocytic leukemia 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; SNHG, small nucleolar RNA host gene; CRNDE, Colorectal neoplasia differentially expressed; FIRRE, functional intergenic repeating RNA element; Gas5, growth arrest-specific transcript 5. MEG3, maternally expressed 3; PCAT19, prostate cancer associated transcript 19; TLR5, toll like receptor 5; STAT3, signal transducer and activator of transcription 3; TNFAIP1, TNF alpha induced protein 1; AQP9, aquaporin 9; HMGB1, high mobility group box 1; ZEB2L, zinc finger E-box binding homeobox 2; PDCD4, programmed cell death 4; CELF2, CUGBP Elav-like family member 2; SRPK1, SRSF protein kinase 1; CDK5, cyclin dependent kinase 5; WNT5A, Wnt family member 5A; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C motif chemokine receptor 4; JMJD1A, lysine demethylase 3A.

Table 4 Differential Expression of lncRNAs in CCI Model. GENE

Model	Name of lncRNAs	Expression and Significance	Pathway/ Receptor	Biological Function	Tissue	Species	Gender	Ref.
DNP	BC168687	↑ -	TRPV1	It could increase diabetic neuropathic pain by acting TRPV1 receptor	DRG	Rat	Male	[83]
DNP	BC168687	↑ **	P2X7	BC168687 could increase the release of NO and the activation of SGCs, thus regulate the excitability of DRG neurons and the pain behaviors	DRG	Rat	Male	[84]
DNP	NONRATT021972	↑ **	P2X3	It could aggravate thermal and mechanical hyperalgesia vis activating P2X3 receptor of ERK1/2	DRG	Rat	Male	[85]
DNP	NONRATT021972	↑ ***	P2X7	It can increase the expression levels of P2X7 and activation of satellite glial cells in DRG	DRG	Rat	-	[86]
DNP	uc.48+	↑ **	P2X3	uc.48+ may regulate the excitatory of primary sensory neurons by the P2X3 receptor	DRG	Rat	Male	[87]
DNP	uc.48+	↑ **	p38 and ERK1/2	lncRNA uc.48+ may regulate DNP by promoting the release of CGRP	L4-L5 spinal cords	Rat	Male	[88]

Notes: ** Means P < 0.01, and *** means P < 0.001. “-” indicates no mention in the article.

Abbreviation: TRPV1, transient receptor potential cation channel subfamily V member 1.

neuroinflammation and microglia activation are critical in origination and development of DNP. Therefore, these related lncRNAs may become noteworthy targets for the treatment of DNP in the future.

Other Neuropathic Pain Models

Moreover, lncRNAs are found to be actively involved in other models (Table 5). Trigeminal neuralgia (TN) is also a prevalent neuropathic pain in clinical practice. Cai et al found that lncRNA Gm14461 is related to the activation and autophagy of astrocytes in a mouse model of trigeminal neuralgia. When the lncRNA was silencing, loss of Gm14461 increased autophagy in astrocytes and played an analgesic effect by regulating AMPK and Akt/mTOR signaling pathways.⁸⁹ LncRNA Gm14461 is also a factor to regulate CGRP (calcitonin gene-related peptide) and P2X3/7 receptors, which affect the release of inflammatory mediators and pain.⁹⁰ Similar to the role of lncRNA uc.48+ in the DNP model, in the TN model, lncRNA uc.48+ will up-regulate the expression of P2X7 receptors and enhance the phosphorylation of ERK1/2 in the trigeminal nerve meridian, which will heighten pain sensitization.⁹¹ In the rat brachial plexus injury (BPI) model, the expression of lncRNA Malat1 decreases in the spinal cord, which may affect the excitability of neurons by regulating the level of calcium ions.⁹² In addition, up-regulation of JHDM1D-AS1 can reduce the inflammation and neuronal damage of the spinal cord after brachial plexus injury by targeting miR-101-3p-DUSP.⁹³ In the rat model of cancer pain, the expression of lncRNA-NONRATT021203.2 was increased, which can participate in the production of pain by targeting CXCL9 (C-X-C motif chemokine ligand 9).⁹⁴ Postherpetic neuralgia (PHN) is also a considerable neuropathic pain. It confirmed that KCNA2-AS is highly expressing in the spinal cord of the PHN (postherpetic neuralgia) rat model. The pain is relieved when KCNA2-AS was knocking out. The possible reason is that it reduces the translocation of pSTAT3 to the nucleus and inhibits the activation of astrocytes.⁹⁵ However, lncRNA NEAT1 can target the expression of AQP4 by inhibiting miR-128-3p in the rat SCI model, which affects the development of neuropathic pain.⁹⁶ SNI (spare nerve injury) model as a common model in neuropathic pain research. But there are few reliable studies of lncRNAs in this model. Silencing of LINC01119 can alleviate the hypersensitivity and reduced the increase in IL-6, IL-1 β , and TNF- α via binding with ELAVL1 and increasing BDNF mRNA stability and expression level. Here, we briefly reviewed recent studies

of lncRNAs in neuropathic pain, focusing on different rodent neuropathic pain models. Many expressions of lncRNAs are altered in rodent rats after the establishment of chronic pain. Therefore, lncRNAs might be a good potential therapeutic target for neuropathic pain.

Discussion and Future Perspectives

Chronic neuropathic pain is a severe situation, accompanying by injury and dysfunction of the somatosensory nervous system.⁶ However, at present, a lack of efficient curative treatments remains a severe challenge for neuropathic pain. It proved that the rodent models of chronic neuropathic pain play an essential role in parent studies. And detailed intermolecular interactions such as lncRNAs and miRNAs were revealed, which could provide therapeutic promise for the treatment of chronic neuropathic pain.

With the advance in sequencing technology, the studies of lncRNAs in have become a hotspot of the filed. It has been demonstrated that played an essential role in neuropathic pain. Therefore, lncRNAs are likely expected to become a potential target for neuropathic pain. We wonder if these sequencing results of lncRNAs are reliable. For instance, even within the same model there are major differences among sequencing studies published in the literature. The sequencing technology should exhibit excellent sensitivity, repeatability, and stability. In other words, the current study confirms that lncRNAs lack specificity in different models. Perhaps due to complex influencing factors in the system, a few discrepancies are evident in the sequencing results.

As is well known, lncRNAs do not participate in protein-coding directly. However, it plays an imperative part in co-transcriptional regulation, post-transcriptional and Post-translational protein modifications and so on.²⁰ Related research found that the potential regulatory effect of lncRNAs is very distinguished in various diseases. In the above experiments of different neuropathic pain animal models, but also present a significant role in regulating the generation as well as the progression of neuropathic pain. The previous focus was mainly on the changes in the excitability of central and peripheral sensory neurons and the interaction of surrounding microglia, macrophages and other immune cells in the research of neuropathic pain, which led to the persistence of pain signals. What's more, we have shown in this review that the interactions of the lncRNAs, miRNA and proteins are very complicated. As such, the studies of those non-coding RNAs can be used to

Table 5 Differential Expression of lncRNAs in Other Models

Model	Name of lncRNAs	Location of the Gene	Expression and Significance	Pathway/ Receptor	Biological Function	Tissue	Species	Gender	Ref.
TN	Gm14461	Chromosome2 2 C3; 2	↑ **	AMPK and Akt/mTOR signaling	Gm14461 silencing relieves mechanical withdrawal threshold and inhibits astrocyte activation and enhances autophagy via regulating of the AMPK and Akt/mTOR signaling	Trigeminal ganglia	Mice	-	[89]
TN	Gm14461	Chromosome2 2 C3; 2	↑ *	CGRP and P2X3/7 receptor	Gm14461 overexpression decreases MWT and upregulates mRNA levels of proinflammatory cytokine and protein levels of CGRP and P2X3/7 receptor	Trigeminal ganglia	Mice	-	[90]
TN	uc.48+	/	↑ **	P2X7/ ERK1/2	uc.48+ can activate the P2X7 receptor to regulate the MWT	Trigeminal ganglia	Rat	Male	[91]
BPI	Malat1	/	↓ *	Unknown	Down-regulation of Malat1 increases the frequency of spontaneous electric activity via changing of intracellular calcium concentration in neurons but have no effect on neuronal apoptosis.	C5-T1 spinal cord	Rat	Male	[92]
CIP	NONRATT021203.2	/	↑ *	CXCL9	LncRNA-NONRATT021203.2 could target CXCL9 to regulate hyperalgesia	DRG	Rat	Female	[94]
PHN	KCNA2	Chromosome 2 2q34	↓ **	STAT3	KCNA2-AS relieved mechanical allodynia partly by combining with pSTAT3 to regulate cytoplasmic/nuclear translocation.	Spinal cord	Rat	Female	[95]
SCI	NEAT1	/	↑ ***	miR-128-3p/AQP4 axis	Over-expression of NEAT1 enhance the expression of inflammatory factors (IL-6, IL-1 β , and TNF α)	Spinal cord	Rat	Female	[96]
SCI	PVT1	Chromosome 6 7q33	↑ ***	miR-186-5p/CXCL13/CXCR5 Axis	PVT1 depletion could alleviated pain behaviors, astrocytic activation and reduced the expression of neuroinflammatory cytokine	T10 spinal cord	Rat	Male	[97]
BPI	JHDM1D-ASI	Chromosome 6 4q22	↓ ***	miR-101-3p/DUSP1 axis	JHDM1D-ASI have a neuroprotective effect by suppressing neuronal apoptosis and microglial activation	Spinal cord	Rat	-	[93]
SNI	LINC01119	Chromosome 6 2p21	↑ **	ELAVL1/ BDNF	Silencing of LINC01119 can alleviate the hypersensitivity and reduced the increase in IL-6, IL-1 β , and TNF- α via binding with ELAVL1 and increasing BDNF mRNA stability and expression level.	L4-L5spinal cord; serum	Rat; Human	Male	[98]

Notes: "/" Means no related location of genes were found in specific genera but it does not means absent. * means $P < 0.05$, ** means $P < 0.01$, and *** means $P < 0.001$; "-" indicates no mention in the article.

Abbreviations: TN, trigeminal neuralgia; BPI, brachial plexus injury; PHN, post-herpetic neuralgia; SCI, spinal cord injury; PHN, postherpetic neuralgia; CIP, Cancer-induced pain; MWT, mechanical withdrawal threshold; SNI, spare nerve injury; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; PVT1, plasmacytoma variant translocation 1; KCNA2-AS, KCNA2 antisense RNA; NEAT1, Nuclear paraspeckle assembly transcript 1; JHDM1D-ASI, JHDM1D antisense 1; Mtor, mechanistic target of rapamycin kinase; STAT3, signal transducer and activator of transcription 3; DUSP1, dual specificity phosphatase 1; ELAVL1, ELAV like RNA binding protein 1; BDNF, brain derived neurotrophic factor.

understand better the mechanisms of molecular interaction. Current works of lncRNAs have been shown in Figure 2. However, there is limited research focused on clinical prospective studies of lncRNAs in neuropathic pain. Because of neurocytes are nonrenewable, human specimens are generally available. Currently, several researches are focusing attention on the animal and cell studies.

Gender differences of immune cells were found among the neuropathic pain. The magnitude of the injury-induced macrophage expansion was different between the female and male mice.¹⁶ Microglia also showed sex differences. It is critical to the development of the neuropathic pain in male mice but not in female.⁹⁹ No previous studies have, however,

investigated the differentially expressed lncRNAs in neuropathic pain models of different sex. The exact role of lncRNAs in mediating hypersensitivity in sexually dimorphic is still to be defined in the in the subsequent studies.

In conclusion, current results of lncRNAs in neuropathic pain indicate the potential of using sequencing technology. Despite the current researches lacking clinical implications and specificity of lncRNAs in different models, sufficient evidence has been presented to prove that lncRNAs have critical roles in the development of neuropathic pain. Therefore, additional studies are required to look for potential specific biomarkers and treatment in neuropathic pain from basic research to clinical applications.

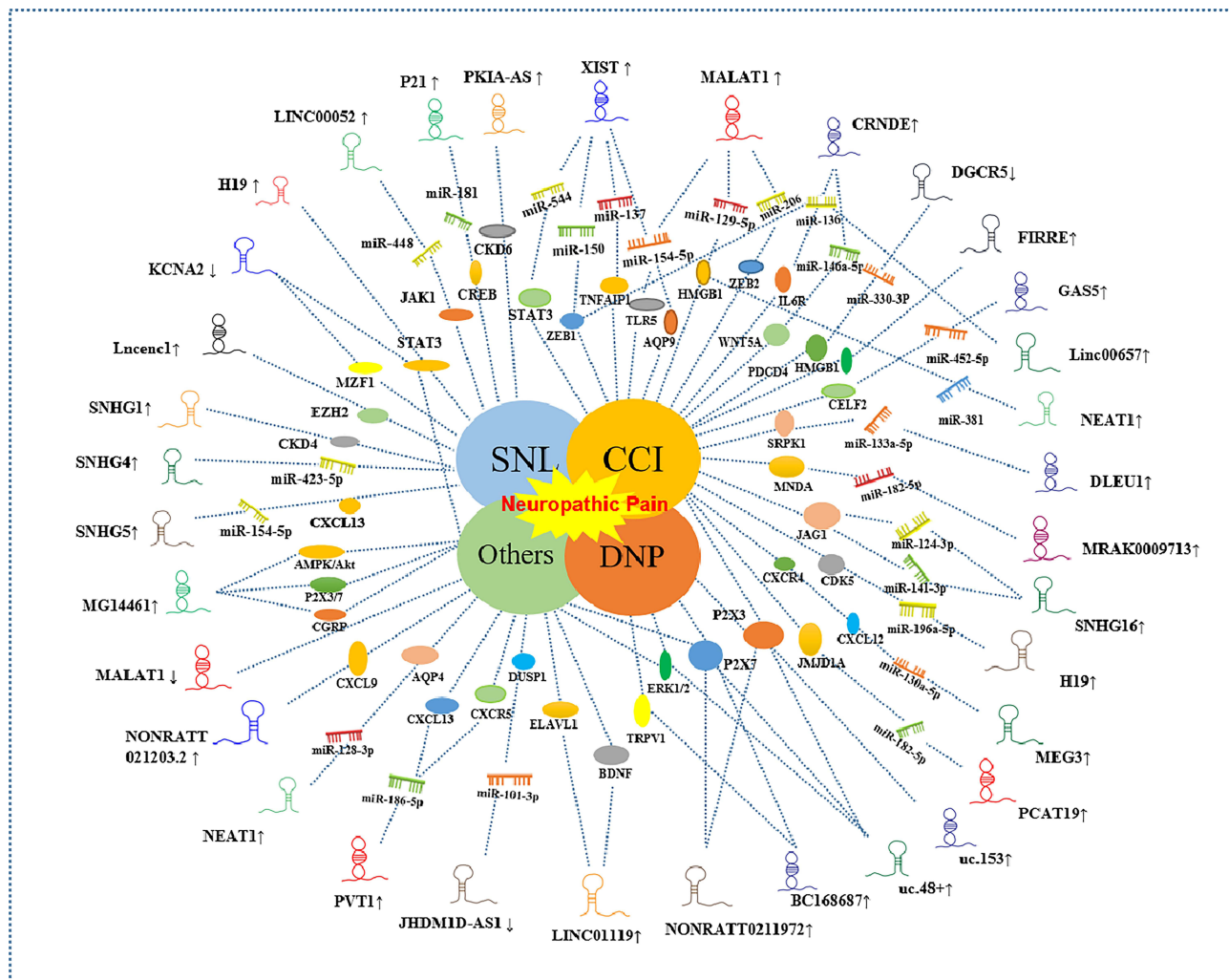


Figure 2 Differentially expressed lncRNA in differential neuropathic pain models. ↑: up-regulation; ↓: down-regulation. Differential shapes of lncRNAs denote gene symbol without biological meaning. Center works represent different models of neuropathic pain.

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Author Contributions

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Disclosure

The authors have no conflicts of interest to declare.

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