

REVIEW

Emerging roles of circular RNAs in neuropathic pain

Derong Xu¹ | Xuexiao Ma¹ | Chong Sun¹ | Jialuo Han¹ | Chuanli Zhou¹  |
Matthew T. V. Chan² | William K. K. Wu^{2,3}

¹Department of Spine Surgery, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

²Department of Anaesthesia and Intensive Care and Peter Hung Pain Research Institute, The Chinese University of Hong Kong, Hong Kong, China

³State Key Laboratory of Digestive Diseases, LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China

Correspondence

Chuanli Zhou, Department of Spine Surgery, The Affiliated Hospital of Qingdao University, Qingdao, 266000, Shandong, China.
Email: justin_5257@hotmail.com

Abstract

Neuropathic pain is a major type of chronic pain caused by the disease or injury of the somatosensory nervous system. It afflicts about 10% of the general population with a significant proportion of patients' refractory to conventional medical treatment. This highlights the importance of a better understanding of the molecular pathogenesis of neuropathic pain so as to drive the development of novel mechanism-driven therapy. Circular RNAs (circRNAs) are a type of non-coding, regulatory RNAs that exhibit tissue- and disease-specific expression. An increasing number of studies reported that circRNAs may play pivotal roles in the development of neuropathic pain. In this review, we first summarize circRNA expression profiling studies on neuropathic pain. We also highlight the molecular mechanisms of specific circRNAs (circHIPK3, circAnks1a, ciRS-7, cZNRANB1, circZNF609 and circ_0005075) that play key functional roles in the pathogenesis of neuropathic pain and discuss their potential diagnostic, prognostic, and therapeutic utilization in the clinical management of neuropathic pain.

1 | INTRODUCTION

Neuropathic pain is a chronic pain condition caused by disease or injury of the somatosensory nervous system.¹⁻⁵ It encompasses aetiologically distinct yet mechanistically similar disease entities, including postherpetic neuralgia, trigeminal neuralgia, painful diabetic neuropathy, cancer-related and chemotherapy-induced neuropathic pain, and neural injury or impingement, such as spinal cord injury and nerve root compression.⁶⁻¹¹ Although the exact prevalence of neuropathic pain varies from country to country, it has been estimated that up to 10% of the general population is afflicted with this potentially disabling condition.¹²⁻¹⁶ Different medical treatments (eg tricyclic antidepressants, selective serotonin noradrenaline reuptake inhibitors, opioids, lidocaine) have been used clinically for the treatment of neuropathic pain, but up to half of the patients with neuropathic pain are refractory to these drugs.¹⁷⁻²² The ineffectiveness of medical interventions arises partly due to the poorly understood molecular mechanism of neuropathic pain. Both peripheral and

central sensitization are known to be implicated in the pathogenesis of neuropathic pain.²³⁻²⁵ Whereas the anomalous excitability of the primary sensory neurons during peripheral sensitization may be due to maladaptive changes in the gene transcription and translation of enzymes, receptors, and voltage-dependent ion channels in the dorsal root ganglion, neuroinflammation caused by pathological microglia activation takes a major part in the process of central sensitization.²⁶⁻²⁹ However, how the deranged molecular pathways underlying peripheral and central sensitization could be targeted therapeutically is still an active area of investigation.

Circular RNAs (circRNAs) are a type of non-coding, regulatory RNAs evolutionarily conserved across mammalian species.³⁰⁻³⁴ CircRNAs exhibit brain region-specific expression,^{35,36} and the abundance of circRNAs in the brains of various species are largely similar.³⁷⁻⁴⁰ CircRNAs exert their biological functions principally by acting as competing endogenous RNAs (ceRNAs) to regulate gene expression post-transcriptionally by sponging microRNAs (miRNAs).⁴¹⁻⁴⁴ CircRNAs have been shown to be deregulated in different

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. *Cell Proliferation* published by John Wiley & Sons Ltd.

human diseases, including neurological disorders.^{45,46} Recently, studies found that circRNAs may play important roles in the development of neuropathic pain.^{47,48}

In our review, we firstly summarize circRNA expression profiling studies on neuropathic pain so as to provide the scientific community with a comprehensive collection of data sets for subsequent integrative analysis. The biological functions and molecular mechanisms of specific circRNAs involved in the pathogenesis of neuropathic pain are also discussed in relation to their diagnostic, prognostic and therapeutic potentials in clinical settings.

2 | CIRC RNA EXPRESSION PROFILING AND INTEGRATIVE ANALYSIS IN NEUROPATHIC PAIN

Microarray is an efficient tool for circRNA profiling. Cao and colleagues inflicted chronic constriction injury (CCI) to the sciatic nerve of rats to induce neuropathic pain.⁴⁹ They then extracted total RNA from ipsilateral spinal dorsal horns of CCI and sham-operated rats and performed circRNA microarray to analyse circRNA expression patterns. They found that there were 469 differentially expressed circRNAs (363 upregulated and 106 downregulated) in the CCI group compared to the sham-operated group. The expression levels of three circRNAs (circRNA_003724, circRNA_008008 and circRNA_013779) were increased by more than 10 folds after CCI. Furthermore, reverse transcription-quantitative PCR (RT-qPCR) was used to confirm the deregulation of circRNA_008973, circRNA_013779, circRNA_008646, circRNA_35215, circRNA_011111, circRNA_007419, circRNA_007512 and circRNA_010913. CeRNAs network reconstruction indicated that circRNA_013779 and circRNA_008008 are the two key nodes in the circRNA-miRNA interaction network amongst the top 10 differentially expressed circRNAs. Cao and colleagues also performed the circRNA microarray to identify differentially expressed circRNAs in the postherpetic neuralgia (PHN) skin and the control skin.⁵⁰ They showed that only circRNA_405463 showed differential expression when fold change cut-off was set as ≥ 2.0 between the PHN and control group. With a less stringent cut-off (fold change ≥ 1.5), the number of downregulated and upregulated circRNAs increased to 8 and 23, respectively. They also performed miRNA microarray on the same set of samples, which identified of 317 differently expressed miRNAs in the PHN skin (fold change ≥ 2.0). To learn the functions of these differential miRNAs, their potential target mRNAs were predicted and analysed by Genomes pathway, Kyoto Encyclopaedia of Genes (KEGG) and Gene Ontology (GO) enrichment analysis. Target mRNAs were found to be enriched in pathways such as AMP-activated protein kinase (AMPK), mitogen-activated protein kinase (MAPK) and forkhead box O (FoxO) signalling.

With the advancement of linear RNA depletion and bioinformatic workflow, circRNAs have been increasingly profiled by RNA sequencing. Zhou and colleagues performed RNA sequencing to

profile the expression levels of non-coding RNAs (ncRNAs) in the spinal cord after spared nerve injury (SNI)-induced neuropathic pain.⁴⁸ They showed that 188 circRNAs were differentially expressed (68 upregulated and 120 downregulated) in the rat spinal cord on day 14 after SNI as compared to the control group. There were also 144 differentially expressed lncRNAs (15 upregulated and 129 downregulated) and 12 differentially expressed miRNAs (6 upregulated and 6 downregulated), and 1066 differentially expressed mRNAs (531 upregulated and 535 downregulated) in the rat spinal cord after SNI at the same time point, in which circ_0006928-miR-184 and LNC_001457-miR-184 interactions were verified to play a crucial role in excessive neuronal cell apoptosis in the spinal cord after SNI. Zhang and colleagues also performed RNA sequencing to profile circRNA expression in the rat spinal dorsal horn on day 7 and day 14 after spinal nerve ligation (SNL).⁵¹ They identified a total of 61,833

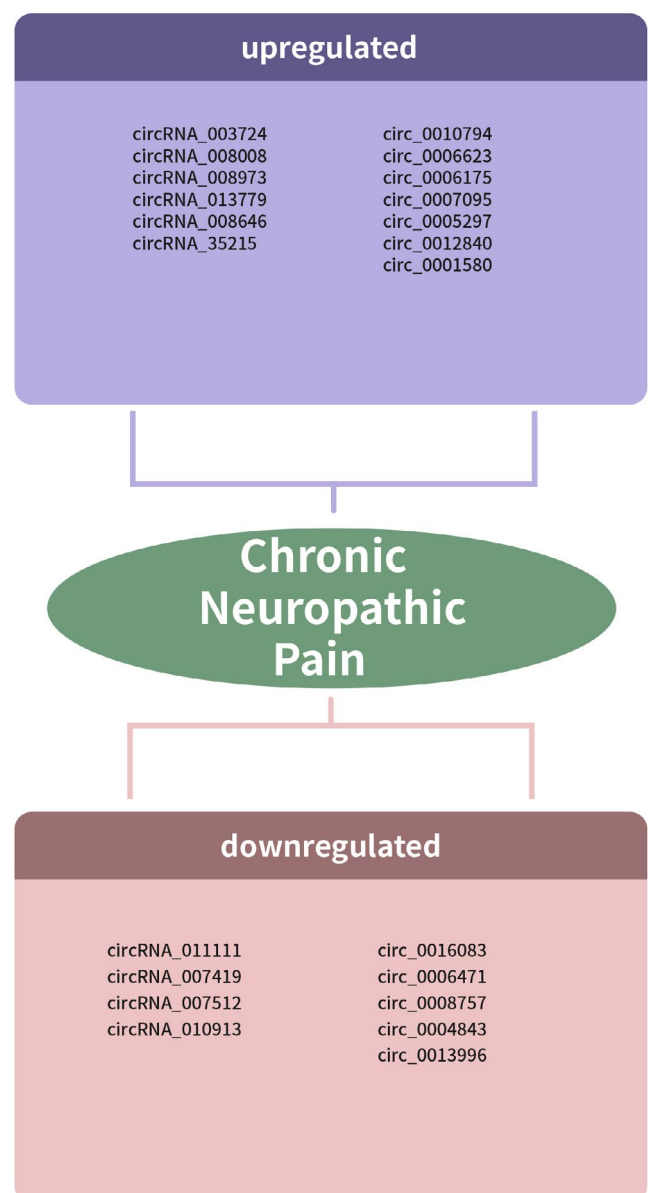


FIGURE 1 Dysregulated circRNAs in neuropathic pain

TABLE 1 CircRNAs expression profiles in neuropathic pain

Num	Method	Sample	Upregulated	Downregulated	References
1	Microarray PCR	Ipsilateral spinal dorsal horns	363 circRNAs circRNA_003724, circRNA_008008 circRNA_008973 circRNA_013779 circRNA_008646, circRNA_35215	106 circRNAs circRNA_011111, circRNA_007419, circRNA_007512 and circRNA_010913	49
2	Microarray	Postherpetic neuralgia skin	66 CircRNAs	68 CircRNAs	50
3	RNA sequencing	Spinal cord	68 circRNAs	120 circRNAs	48
4	RNA sequencing	Spinal dorsal horn	54 circRNAs	52 circRNAs	51
5	RNA sequencing	Spinal cord	64 circRNAs circ_0010794, circ_0006623, circ_0006175, circ_0007095, circ_0005297, circ_0012840 circ_0001580	71 circRNAs circ_0016083, circ_0006471, circ_0008757, circ_0004843 circ_0013996	52

distinct circRNAs according to the criterion of at the least one back spliced junction reads. Amongst them, the reads per million mapped reads (RPM) of 12,849 circRNAs was greater than 0.1. However, only 21 circRNAs were identified to be significantly deregulated with >2.5-fold change at both time points.

Recently, He et al. performed RNA sequencing to study the expression patterns of circRNAs, lncRNAs and miRNAs in the spinal cord of streptozotocin-induced diabetic neuropathic pain (DNP) mice.⁵² They found that there were 135 circRNAs were differentially expressed and 71 circRNAs were downregulated and 64 circRNAs were overexpressed in spinal cord between control group and DNP group. Amongst these, circ_0010794, circ_0006623, circ_0006175, circ_0007095, circ_0005297, circ_0012840 and circ_0001580 was overexpressed and circ_0016083, circ_0006471, circ_0008757, circ_0004843 and circ_0013996 was downregulated (Figure 1 and Table 1).

3 | FUNCTIONS AND MECHANISMS OF ACTION OF NEWLY DISCOVERED CIRC RNAs IN NEUROPATHIC PAIN

3.1 | CircHIPK3

CircHIPK3 is a circRNA that has been shown to function as a tumour suppressor gene or oncogene in a context-dependent manner to modulate tumour progression through sponging miRNAs.⁵³⁻⁵⁵ Wang and colleagues investigated the potential regulatory role of circHIPK3 in the development of diabetic neuropathic pain.⁵⁶ Their data showed that circHIPK3 abundance was increased in the dorsal root ganglion from streptococci-induced diabetic rats and serum from patients with diabetic neuropathic pain. Higher expression of circHIPK3 was positively correlated with the grade neuropathic pain in cases with type 2 diabetes. Functionally, knockdown of circHIPK3 alleviated neuropathic pain in the diabetic rats and suppressed interleukin (IL)-12, tumour necrosis factor (TNF)- α , IL-1 β and IL-6. Moreover, they showed that circHIPK3 was found to sponge miR-124 to contribute to neuroinflammation and exacerbate neuropathic pain in the diabetic rats. Therefore, circHIPK3 may be a potential therapeutic target for the treatment of neuropathic pain.

3.2 | CircAnks1a

Zhang and colleagues identified the aberrant upregulation of circAnks1a in the rat spinal dorsal horn after SNL by RNA sequencing.⁵¹ CircAnks1a was found to be localized in both the nucleus and cytoplasm. Knockdown of circAnks1a attenuated the pain-like behaviour caused by SNL. Mechanistically, circAnks1a increased the interaction between transportin-1 and transcription factor YBX1 and thereby inducing the nuclear translocation of YBX1 from the cytoplasm. CircAnks1a also directly bind to Vegfb promoter and promoted YBX1 recruitment to facilitate transcription of *Vegfb*.

Moreover, cytoplasmic circAnks1a acted as a miRNA sponge to repress miR-324-3p to disinhibit VEGFB. Overexpression of VEGFB contributed to the increased excitability of the dorsal horn neurons and SNL-induced pain. These data suggested that the circAnks1a-miR-324-3p-VEGFB axis is a novel therapeutic target in neuropathic pain.

3.3 | ciRS-7

The circRNA ciRS-7 has been found to take part in the development of different diseases.⁵⁷⁻⁶⁰ For example, Han and colleagues demonstrated that ciRS-7 induced migration and growth through modulating the miR-7-EGFR axis in papillary thyroid cancer.⁶¹ Zhang and colleagues also showed that ciRS-7 enhanced epithelial-mesenchymal transition through sponging miR-641 to derepress MDM2 and ZEB1 expression.⁶² In the CCI model of neuropathic pain, Cai et al. found that ciRS-7 expression in the rat spinal cord dorsal horn was positively correlated with development of neuropathic pain partly through promoting inflammation, in which knockdown of ciRS-7 attenuated microglia activation and expression of pro-inflammatory cytokines IL-6, IL-12 and TNF α .⁶³ Mechanistically, ciRS-7 bound to and increased the availability of miR-135a-5p, whose inhibition also mitigated neuroinflammation and neuropathic pain. Their data indicated that either targeting ciRS-7 or miR-135a-5p could alleviate neuropathic pain through suppressing neuroinflammation.

3.4 | cZNRANB1

Wei and colleagues studied the expression and functional role of miR-24-3p in the development of neuropathic pain in the CCI rat models.⁶⁴ They found that miR-24-3p expression was upregulated in the dorsal spinal cords of CCI rats, in which ablation of miR-24-3p significantly alleviated thermal hyperalgesia and mechanical allodynia. Moreover, miR-24-3p upregulated Wnt5a- β -catenin signalling

pathway to induce neuropathic pain by inhibiting LPAR3 expression. As the upstream modulator, the circRNA cZNRANB1 was found to sponge miR-24-3p as predicted by bioinformatics analysis and confirmed by luciferase reporter assay and biotinylated RNA pull-down. Importantly, cZNRANB1 expression was decreased in CCI rats, in which enforced expression of cZNRANB1 alleviated thermal hyperalgesia and mechanical allodynia. The regulation of miR-24-3p-LPAR3 axis by cZNRANB1 was also confirmed in the CCI model.

3.5 | CircZNF609

Li and colleagues demonstrated that the expression of miR-22-3p was downregulated in the dorsal spinal cord of CCI rats at the post-operative day 0, 3, 7, 10 and 14 as compared to the sham-operated rats.⁶⁵ Enforced expression of miR-22-3p attenuated neuropathic pain and suppressed the expression of pro-inflammatory cytokines IL-6, TNF- α and IL-1. Moreover, ENO1 was identified to be a direct target gene for miR-22-3p. Downregulation of miR-22-3p alleviated the thermal hyperalgesia and mechanical allodynia partly through targeting ENO1 expression. They also showed that the circRNA circZNF609, which was upregulated in CCI rats, was a sponge for miR-22-3p. Functionally, knockdown of circZNF609 alleviated thermal hyperalgesia and mechanical allodynia levels and suppressed IL-6, TNF- α and IL-1 expression by regulating miR-22-3p-ENO1 axis. These data suggested that circZNF609 induced inflammation factors to mediate central sensitization in neuropathic pain development through regulating miR-22-3p-ENO1 axis.

3.6 | Circ_0005075

circ_0005075 deregulation has been implicated in cancer development.⁶⁶⁻⁷⁰ Zhang and colleagues showed that circ_0005075 was upregulated in the dorsal spinal cord of CCI rats, in which knockdown of circ_000507 suppressed neuropathic pain behaviours such

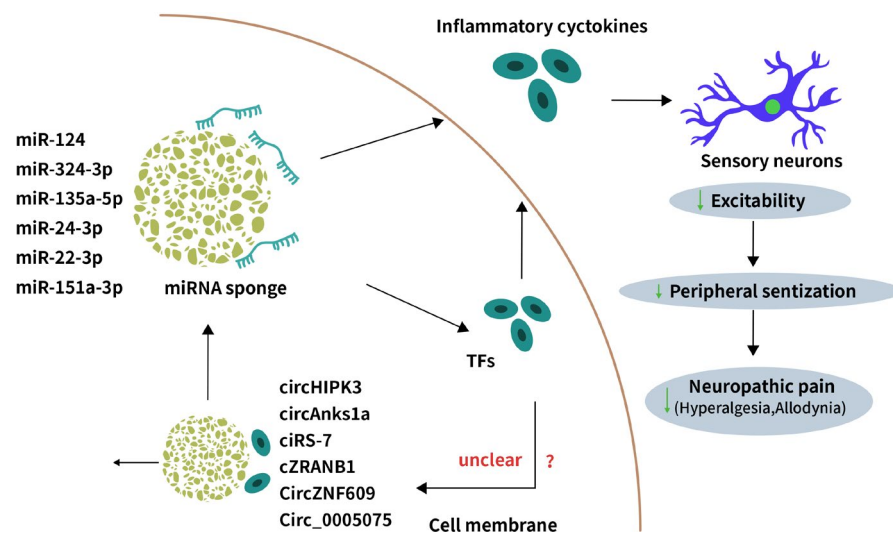


FIGURE 2 Schematic of circRNA-miRNA interactions in neuropathic pain. circRNAs functions as 'miRNA sponge' to reduce the expression levels of miRNA in NP, it prevents TFs (such as TNFAIP1, ZEB1, STAT3) from microRNA-mediated suppression, or directly decrease the release of inflammatory cytokines, thus alleviating the symptoms of neuropathic pain

oligonucleotides or small interfering RNAs-mediated knockdown; and (3) steric blockade of circRNA-miRNA interactions by morpholinos. Through circRNA microarray and RNA sequencing, a growing number of deregulated circRNAs are expected to be identified in neuropathic pain. The potential implications in the clinical diagnosis and prognostication of circRNAs in neuropathic pain will be achieved. Then, it needs to measure these deregulated circRNAs in large samples of neuropathic pain. However, unlike other ncRNAs, such as long non-coding RNAs (lncRNA), the correlation between pain scores of patients and circRNA levels in the plasma has not yet to be demonstrated. Further research in this direction will help identify novel biomarkers for monitoring patients with neuropathic pain. However, more in-depth functional and mechanistic investigations on pain-related circRNAs are warranted. It is hopeful that, with more translational studies, circRNAs will one day be utilized for the clinical management of patients with neuropathic pain.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

DRX, XXM, CS, JL H, CLZ: drafted and wrote the manuscript. MTVC and WKKW: revised the manuscript. DRX and CLZ: participated in the design of the review. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Chuanli Zhou  <https://orcid.org/0000-0003-4593-2170>

REFERENCES

- Zhang K, Wang J, Xi H, Li L, Lou Z. Investigation of neuroprotective effects of erythropoietin on chronic neuropathic pain in a chronic constriction injury rat model. *J Pain Res.* 2020;13:3147-3155.
- Zhao LX, Jiang M, Bai XQ, et al. TLR8 in the trigeminal ganglion contributes to the maintenance of trigeminal neuropathic pain in mice. *Neurosci Bull.* 2021;37(4):550-562.
- Zhang Z, Zheng B, Du S, et al. Eukaryotic initiation factor 4 gamma 2 contributes to neuropathic pain through down-regulation of Kv1.2 and the mu opioid receptor in mouse primary sensory neurones. *Br J Anaesth.* 2021;126(3):706-719.
- Zhang JY, Lv DB, Su YN, et al. LncRNA SNHG1 attenuates neuropathic pain following spinal cord injury by regulating CDK4 level. *Eur Rev Med Pharmacol Sci.* 2020;24(23):12034-12040.
- Yu Z, Liu J, Sun L, Wang Y, Meng H. Combination of botulinum toxin and minocycline ameliorates neuropathic pain through antioxidant stress and anti-inflammation via promoting SIRT1 pathway. *Front Pharmacol.* 2020;11:602417.
- Yoon SY, Roh DH, Yeo JH, Woo J, Han SH, Kim KS. Analgesic efficacy of alpha2 adrenergic receptor agonists depends on the chronic state of neuropathic pain: role of regulator of G protein signaling 4. *Neuroscience.* 2021;455:177-194.
- Yeh TY, Luo IW, Hsieh YL, Tseng TJ, Chiang H, Hsieh ST. Peripheral neuropathic pain: from experimental models to potential therapeutic targets in dorsal root ganglion neurons. *Cells.* 2020;9(12).
- Yao L, Guo Y, Wang L, et al. Knockdown of miR-130a-3p alleviates spinal cord injury induced neuropathic pain by activating IGF-1/IGF-1R pathway. *J Neuroimmunol.* 2021;351:577458.
- Xian S, Ding R, Li M, Chen F. LncRNA NEAT1/miR-128-3p/AQP4 axis regulating spinal cord injury-induced neuropathic pain progression. *J Neuroimmunol.* 2021;351:577457.
- Wu Y, Gu Y, Shi B. miR-590-3p Alleviates diabetic peripheral neuropathic pain by targeting RAP1A and suppressing infiltration by the T cells. *Acta Biochim Pol.* 2020;67(4):587-593.
- Wen W, Wang J, Zhang B, Wang J. PPARalpha agonist WY-14643 relieves neuropathic pain through SIRT1-mediated deacetylation of NF-kappaB. *PPAR Res.* 2020;2020:6661642.
- Wang X, Tian S, Wang H, et al. Botulinum toxin type A alleviates neuropathic pain and suppresses inflammatory cytokines release from microglia by targeting TLR2/MyD88 and SNAP23. *Cell Biosci.* 2020;10(1):141.
- Wang Q, Lin J, Yang P, et al. Effect of massage on the TLR4 signalling pathway in rats with neuropathic pain. *Pain Res Manage.* 2020;2020:8309745.
- Wang M, Cai X, Wang Y, et al. Astragaline alleviates neuropathic pain by suppressing P2X4-mediated signaling in the dorsal root ganglia of rats. *Frontiers Neurosci.* 2020;14:570831.
- Tian Y, Sun L, Qi T. Long noncoding RNA GAS5 ameliorates chronic constriction injury induced neuropathic pain in rats by modulation of the miR-452-5p/CELF2 axis. *Can J Physiol Pharmacol.* 2020;98(12):870-877.
- Sun M, Sun Y, Ma J, Li K. YY1 promotes SOCS3 expression to inhibit STAT3 mediated neuroinflammation and neuropathic pain. *Molec Med Rep.* 2021;23(2).
- Oliveira RAAD, Baptista AF, Sá KN, et al. Clinicians participants of the panel of experts recommended by the Brazilian Academy of N and Andrade DC. Pharmacological treatment of central neuropathic pain: consensus of the Brazilian Academy of Neurology. *Arq Neuropsiquiatr.* 2020;78(11):741-752.
- Ni W, Zheng X, Hu L, Kong C, Xu Q. Preventing oxaliplatin-induced neuropathic pain: Using berberine to inhibit the activation of NF-kappaB and release of pro-inflammatory cytokines in dorsal root ganglions in rats. *Exp Therap Med.* 2021;21(2):135.
- Naccache DD. Cannabis alleviates neuropathic pain and reverses weight loss in diabetic neuropathic cachexia in a previous heroin abuser. *Endocrinol Diabetes Metabol Case Rep.* 2020;2020.
- Moon JY, Lee CS, Yoo Y, Lee S, Lee SH, Lee S. Evaluation of an effectiveness and safety of the electroacupuncture in the management of intractable neuropathic pain: A prospective, open-labeled, randomized, cross-over clinical trial. *Medicine.* 2020;99(51):e23725.
- Liu XH, Du YM, Cong HJ, Liu GZ, Ren YE. Effects of continuous epidural injection of dexamethasone on blood glucose, blood lipids, plasma cortisol and ACTH in patients with neuropathic pain. *Front Neurol.* 2020;11:564643.
- Liu M, Li K, Wang Y, Zhao G, Jiang J. Stem cells in the treatment of neuropathic pain: research progress of mechanism. *Stem Cells Int.* 2020;2020:1-13.
- Gao WS, Qu YJ, Huai J, Wei H, Zhang Y, Yue SW. DOK3 is involved in microglial cell activation in neuropathic pain by interacting with GPR84. *Ageing.* 2020;13(1):389-410.
- Buffon AC, Javornik MA, Heymanns AC, et al. Role of the endocannabinoid system on the antihyperalgesic action of gabapentin in animal model of neuropathic pain induced by partial sciatic nerve ligation. *Anais Da Academia Brasileira De Ciencias.* 2020;92(4):e20191155.
- Alkudhayri S, Sajini R, Alharbi B, et al. Investigating the beneficial effect of aliskiren in attenuating neuropathic pain in diabetic Sprague-Dawley rats. *Endocrinol Diab Metab.* 2021;4(2):e00209.
- Vergne-Salle P, Bertin P. Chronic pain and neuroinflammation. *Joint Bone Spine.* 2021;88(6):105222.

27. Lassen J, Sturmer KH, Gierthmuhlen J, et al. Protective role of natural killer cells in neuropathic pain conditions. *Pain*. 2021;162(9):2366-2375.
28. Livshits G, Kalinkovich A. Specialized, pro-resolving mediators as potential therapeutic agents for alleviating fibromyalgia symptomatology. *Pain Med*. 2021. [Online ahead of print].
29. Mueller C, Ness TJ, Younger JW. Low-dose dextromethorphan for the treatment of fibromyalgia pain: results from a longitudinal, single-blind, placebo-controlled pilot trial. *J Pain Res*. 2021;14:189-200.
30. Chen T, Yang Z, Liu C, et al. Circ_0078767 suppresses non-small-cell lung cancer by protecting RASSF1A expression via sponging miR-330-3p. *Cell Prolif*. 2019;52(2):e12548.
31. Li J, Wang J, Wang Z. Circ_0006768 upregulation attenuates oxygen-glucose deprivation/reoxygenation-induced human brain microvascular endothelial cell injuries by upregulating VEZF1 via miR-222-3p inhibition. *Metab Brain Dis*. 2021. [Online ahead of print].
32. Li Z, Chen X, Xu D, Li S, Chan MTV, Wu WKK. Circular RNAs in nucleus pulposus cell function and intervertebral disc degeneration. *Cell Prolif*. 2019;52(6):e12704.
33. Liang M, Huang G, Liu Z, et al. Elevated levels of hsa_circ_006100 in gastric cancer promote cell growth and metastasis via miR-195/GPRC5A signalling. *Cell Prolif*. 2019;52(5):e12661.
34. Pan G, Mao A, Liu J, Lu J, Ding J, Liu W. Circular RNA hsa_circ_0061825 (circ-TFF1) contributes to breast cancer progression through targeting miR-326/TFF1 signalling. *Cell Prolif*. 2020;53(2):e12720.
35. Zhang Z, Yang B, Huang J, et al. Identification of the protective effect of Polygonatum sibiricum polysaccharide on d-galactose-induced brain ageing in mice by the systematic characterization of a circular RNA-associated ceRNA network. *Pharm Biol*. 2021;59(1):347-366.
36. Bigarre IM, Trombetta BA, Guo YJ, Arnold SE, Carlyle BC. IGF2R circular RNA hsa_circ_0131235 expression in the middle temporal cortex is associated with AD pathology. *Brain Behav*. 2021;11(4):e02048.
37. Li Z, Li X, Xu D, et al. An update on the roles of circular RNAs in osteosarcoma. *Cell Prolif*. 2021;54(1):e12936.
38. Nie H, Wang Y, Liao S, Zhou J, Ou C. The function and mechanism of circular RNAs in gastrointestinal tumours. *Cell Prolif*. 2020;53(7):e12815.
39. Li Z, Li X, Shen J, Zhang L, Chan MTV, Wu WKK. Emerging roles of non-coding RNAs in scoliosis. *Cell Prolif*. 2020;53(2):e12736.
40. Li Z, Ma J, Shen J, Chan MTV, Wu WKK, Wu Z. Differentially expressed circular RNAs in air pollution-exposed rat embryos. *Environ Sci Pollut Res Int*. 2019;26(33):34421-34429.
41. Liu J, Song S, Lin S, et al. Circ-SERPINE2 promotes the development of gastric carcinoma by sponging miR-375 and modulating YWHAZ. *Cell Prolif*. 2019;52(4):e12648.
42. Wang L, Li B, Yi X, Xiao X, Zheng Q, Ma L. Circ_SMAD4 promotes gastric carcinogenesis by activating wnt/beta-catenin pathway. *Cell Prolif*. 2021;54(3):e12981.
43. Zhang J, Hu H, Zhao Y, Zhao Y. CDR1as is overexpressed in laryngeal squamous cell carcinoma to promote the tumour's progression via miR-7 signals. *Cell Prolif*. 2018;51(6):e12521.
44. Li X, Gao F, Fan Y, et al. A novel identified circ-ANKHD1 targets the miR-27a-3p/SFRP1 signaling pathway and modulates the apoptosis of granulosa cells. *Environ Sci Pollut Res Int*. 2021. [Online ahead of print].
45. Liu P, Li X, Guo X, et al. Circular RNA DOCK1 promotes bladder carcinoma progression via modulating circDOCK1/hsa-miR-132-3p/Sox5 signalling pathway. *Cell Prolif*. 2019;52(4):e12614.
46. Ni W, Jiang C, Wu Y, et al. CircSLC7A2 protects against osteoarthritis through inhibition of the miR-4498/TIMP3 axis. *Cell Prolif*. 2021;54(6):e13047.
47. Zhang Y, Gao T, Li X, et al. Circ_0005075 targeting miR-151a-3p promotes neuropathic pain in CCI rats via inducing NOTCH2 expression. *Gene*. 2021;767:145079.
48. Zhou X, Xiong Q, Chen H, Yang C, Fan Y. Identification of the spinal expression profile of non-coding RNAs involved in neuropathic pain following spared nerve injury by sequence analysis. *Front Molec Neurosci*. 2017;10:91.
49. Cao S, Deng W, Li Y, et al. Chronic constriction injury of sciatic nerve changes circular RNA expression in rat spinal dorsal horn. *J Pain Res*. 2017;10:1687-1696.
50. Cao S, Zhang D, Yuan J, et al. MicroRNA and circular RNA expression in affected skin of patients with postherpetic neuralgia. *J Pain Res*. 2019;12:2905-2913.
51. Zhang SB, Lin SY, Liu M, et al. CircAnks1a in the spinal cord regulates hypersensitivity in a rodent model of neuropathic pain. *Nat Commun*. 2019;10(1):4119.
52. He J, Wang HB, Huang JJ, et al. Diabetic neuropathic pain induced by streptozotocin alters the expression profile of non-coding RNAs in the spinal cord of mice as determined by sequencing analysis. *Exp Therap Med*. 2021;22(1):775.
53. Luo N, Liu S, Li X, Hu Y, Zhang K. Circular RNA circHIPK3 promotes breast cancer progression via sponging MiR-326. *Cell Cycle*. 2021;20(13):1320-1333.
54. Xiao L, Ma X-X, Luo J, et al. Circular RNA circHIPK3 promotes homeostasis of the intestinal epithelium by reducing microRNA 29b function. *Gastroenterology*. 2021;161(4):1303-1317.e3. <https://doi.org/10.1053/j.gastro.2021.05.060>
55. Qi L, Sun B, Yang B, Lu S. circHIPK3 (hsa_circ_0000284) promotes proliferation, migration and invasion of breast cancer cells via miR-326. *Oncotargets Therapy*. 2021;14:3671-3685.
56. Wang L, Luo T, Bao Z, Li Y, Bu W. Intrathecal circHIPK3 shRNA alleviates neuropathic pain in diabetic rats. *Biochem Biophys Res Comm*. 2018;505(3):644-650.
57. Su C, Han Y, Zhang H, et al. CiRS-7 targeting miR-7 modulates the progression of non-small cell lung cancer in a manner dependent on NF-kappaB signalling. *J Cell Mol Med*. 2018;22(6):3097-3107.
58. Zhou X, Li J, Zhou Y, et al. Down-regulated ciRS-7/up-regulated miR-7 axis aggravated cartilage degradation and autophagy defecation by PI3K/AKT/mTOR activation mediated by IL-17A in osteoarthritis. *Aging*. 2020;12(20):20163-20183.
59. Zou Y, Zheng S, Deng X, et al. The role of circular RNA CDR1as/ciRS-7 in regulating tumor microenvironment: a pan-cancer analysis. *Biomolecules*. 2019;9(9):429.
60. Sang M, Meng L, Sang Y, et al. Circular RNA ciRS-7 accelerates ESCC progression through acting as a miR-876-5p sponge to enhance MAGE-A family expression. *Cancer Lett*. 2018;426:37-46.
61. Han J-Y, Guo SI, Wei NA, et al. ciRS-7 promotes the proliferation and migration of papillary thyroid cancer by negatively regulating the miR-7/epidermal growth factor receptor axis. *Biomed Res Int*. 2020;2020:9875636.
62. Zhang F, Xu Y, Ye W, Jiang J, Wu C. Circular RNA S-7 promotes ovarian cancer EMT via sponging miR-641 to up-regulate ZEB1 and MDM2. *Biosci Rep*. 2020;40(7).
63. Cai W, Zhang Y, Su Z. ciRS-7 targeting miR-135a-5p promotes neuropathic pain in CCI rats via inflammation and autophagy. *Gene*. 2020;736:144386.
64. Wei M, Li L, Zhang Y, Zhang M, Su Z. Downregulated circular RNA zRANB1 mediates Wnt5a/beta-Catenin signaling to promote neuropathic pain via miR-24-3p/LPAR3 axis in CCI rat models. *Gene*. 2020;761:145038.
65. Li L, Luo Y, Zhang Y, et al. CircZNF609 aggravates neuropathic pain via miR-22-3p/ENO1 axis in CCI rat models. *Gene*. 2020;763:145069.
66. Li MF, Li YH, He YH, et al. Emerging roles of hsa_circ_0005075 targeting miR-431 in the progress of HCC. *Biomed Pharmacotherapy*. 2018;99:848-858.

67. Yang X, Song H, Zi Z, et al. Circ_0005075 promotes hepatocellular carcinoma progression by suppression of microRNA-335. *J Cell Physiol.* 2019;234(12):21937-21946.
68. Zhong D, Li P, Gong PY. Hsa_circ_0005075 promotes the proliferation and invasion of colorectal cancer cells. *Int J Biol Markers.* 2019;34(3):284-291.
69. Jin YD, Ren YR, Gao YX, Zhang L, Ding Z. Hsa_circ_0005075 predicts a poor prognosis and acts as an oncogene in colorectal cancer via activating Wnt/beta-catenin pathway. *Eur Rev Med Pharmacol Sci.* 2019;23(8):3311-3319.
70. Fang DZ, Wang WJ, Li FY, et al. Circ_0005075 stimulates the proliferation and metastasis of glioma via downregulating SIRT1. *Eur Rev Med Pharmacol Sci.* 2020;24(1):258-266.

How to cite this article: Xu D, Ma X, Sun C, et al. Emerging roles of circular RNAs in neuropathic pain. *Cell Prolif.* 2021;54:e13139.<https://doi.org/10.1111/cpr.13139>