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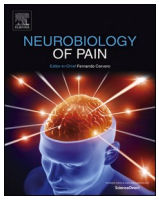

Regulation by noncoding RNAs of local translation, injury responses, and pain in the peripheral nervous system

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ABSTRACT

Neuropathic pain is a chronic condition arising from damage to somatosensory pathways that results in pathological hypersensitivity. Persistent pain can be viewed as a consequence of maladaptive plasticity which, like most enduring forms of cellular plasticity, requires altered expression of specific gene programs. Control of gene expression at the level of protein synthesis is broadly utilized to directly modulate changes in activity and responsiveness in nociceptive pathways and provides an effective mechanism for compartmentalized regulation of the proteome in peripheral nerves through local translation. Levels of noncoding RNAs (ncRNAs) are commonly impacted by peripheral nerve injury leading to persistent pain. NcRNAs exert spatiotemporal regulation of local proteomes and affect signaling cascades supporting altered sensory responses that contribute to hyperalgesia. This review discusses ncRNAs found in the peripheral nervous system (PNS) that are dysregulated following nerve injury and the current understanding of their roles in pathophysiological pain-related responses including neuroimmune interactions, neuronal survival and axon regeneration, Schwann cell dedifferentiation and proliferation, intercellular communication, and the generation of ectopic action potentials in primary afferents. We review progress in the field beyond cataloging, with a focus on the relevant target transcripts and mechanisms underlying pain modulation by ncRNAs.

Introduction

Neuropathic pain is a chronic condition characterized by spontaneous pain and pathologically amplified responses to both noxious and innocuous stimuli (Costigan et al., 2009). These types of hypersensitivity can arise following damage to components of the somatosensory nervous system, for example by peripheral nerve or spinal cord injury, chemotherapeutic toxicity, viral infection, or diabetes (Ducreux et al., 2006; Dworkin et al., 2003). Screening tools have been used to estimate that 7–8 % of adults have chronic neuropathic pain, which presents a serious public health issue accompanied by a socioeconomical burden (Lépine & Briley, 2004; van Hecke et al., 2014). With few effective and tolerable treatments available, there is now a focus on discovery-based science aimed at better understanding the mechanistic underpinnings of neuropathic pain. At a molecular level, pathological pain can be viewed as a consequence of maladaptive plasticity within both nociceptive and non-nociceptive somatosensory pathways. As with other forms of neuroplasticity, the regulation of gene expression and protein synthesis is central to generating the biochemical, structural, and functional changes supporting enduring nociceptive plasticity and persistent pain (Khoutorsky & Price, 2018). Plasticity associated with neuropathic pain can occur both in primary afferent neurons along with the surrounding immune cells and Schwann cells in the peripheral nervous system (PNS), and in the spinal cord dorsal horn, subcortical, and cortical areas of the central nervous system (CNS) that process nociceptive and innocuous somatosensation (Price & Inyang, 2015).

Following injury in the PNS, both injured and uninjured nociceptive neurons respond to neurotrophic factors, secreted cytokines, chemokines, and other inflammatory mediators produced by injured neurons, activated immune cells, and surrounding Schwann cells (Scholz & Woolf, 2007). These inflammatory mediators, including Interleukin-1β (IL1β), tumor necrosis factor (TNF), bradykinin, as well as neurotrophic factors such as nerve growth factor (NGF), can activate intracellular signaling pathways in nociceptive neurons to promote both immediate responses and alterations in gene and protein regulation that underlie enduring nociceptive neuron plasticity (Binshtok et al., 2008; Jin &

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Gereau, 2006; W. Zhu & Oxford, 2007). Alterations in the local expression, trafficking, membrane insertion and kinetics of ion channels and receptors are examples of processes that can modulate membrane excitability in uninjured nociceptive neurons. Ectopic action potentials and altered firing thresholds in nearby intact nociceptive sensory neurons surviving the injury are thought to contribute to ongoing pain and to alterations in sensory responsiveness that manifest as hyperalgesia. Changes in peripheral neuron function can be further accompanied by changes in central sensitization involving facilitation and disinhibition of synaptic transmission, as well as structural changes in synaptic connectivity, which can produce significant nociceptive pain independent of peripheral inputs, or allow pain to be evoked by peripheral neurons that normally evoke only innocuous sensations (Campbell & Meyer, 2006; Obata et al., 2003; Woolf & Salter, 2000). This review, however, will focus on the gene regulatory mechanisms underlying persistent neuronal plasticity in peripheral nerves, and their contributions to the generation of persistent pain. In particular, we will review the emerging understanding and knowledge gaps in mechanisms by which translation is shaped by noncoding RNAs (ncRNAs) to promote enduring changes in neuronal responses that contribute to neuropathic and nociceptive pain.

Regulation of local axonal translation in nociceptive plasticity

Local translation of messenger RNAs (mRNAs) plays essential roles in subcellular protein distribution and contributes to different forms of neuronal plasticity, including synapse formation (Lyles et al., 2006), synaptic plasticity (Huber et al., 2000; Kang & Schuman, 1996; Miller et al., 2002), axon guidance, maintenance and viability (Cioni et al., 2018; Wong et al., 2017; Yoon et al., 2012), as well as nerve regeneration and nociceptor hyper-excitability in response to nerve injury (Khoutorsky & Price, 2018; Koley et al., 2019; Willis & Twiss, 2006). The on-site synthesis of proteins in neuronal processes (i.e., dendrites, axons, and nerve terminals) provides an effective mechanism to achieve high spatial and temporal control of the local proteome (Glock et al., 2017). The presence of mRNAs and translational machinery (ribosomes and translation factors) has been documented in subcellular nociceptive compartments and enables the local generation of proteins in response to upstream translation regulatory pathways (Koley et al., 2019; Steward & Levy, 1982).

The cell bodies of sensory neurons of the PNS are located in dorsal root ganglia (DRG) and trigeminal ganglia (TG) and may be located up to a meter away from the nerve terminals innervating their peripheral target tissues. The local synthesis of protein in nerve processes is a conserved mechanism that ensures neurons can rapidly fulfill local demands for new protein synthesis in nerve processes and at nerve terminals in response to a changing environment (Perez et al., 2021). In the nociceptive system, in particular, neither changes in transcription nor protein trafficking to nerve endings appear to have the dynamics to wholly account for the observed changes in gene expression and phenotypes involved in nociceptive plasticity (Khoutorsky & Price, 2018). Local translation not only provides relatively fast and potentially spatially restricted responses to extracellular stimuli, but also reduces the cellular energy cost and undesired protein interactions accrued during protein trafficking (Holt et al., 2019; Jung et al., 2014). Localized control in distal neuronal compartments enables both proteome homeostatic mechanisms (Holt et al., 2019; Jung et al., 2014), as well as adaptive translation in response to external and intrinsic signaling cues (Jung et al., 2014).

The profiling of RNA and protein contents through RNA sequencing (RNA-seq) and proteomic strategies has demonstrated that nociceptor axonal compartments undergo robust changes in mRNA and protein composition following nerve injury, which participate in the development of persistent nociceptive hyper-excitability (Hirai et al., 2017; H.-L. Huang et al., 2008). In particular, injured peripheral sensory axons have been shown to become enriched for mRNAs with longer 3′ untranslated regions (UTRs), an effect which might be expected to enhance potential for regulated translation (Hirai et al., 2017). ^{35}S methionine labeling of de novo synthesized proteins in nerve terminals has been used to confirm the local production of axonal proteins, as well as to reveal that, following peripheral nerve injury, axons produce a repertoire of proteins distinct from that of neuronal somata in the DRG (H.-L. Huang et al., 2008). While high throughput studies have documented a large variety of mRNAs present in peripheral nerve compartments such as the sciatic nerve (Hirai et al., 2017), not all mRNAs appear to be translated in response to nerve injury, as illustrated by proteomic studies (H.-L. Huang et al., 2008). Collectively, these findings raise interest in understanding the molecular mechanisms shaping the local complement of proteins produced following peripheral nerve injury through selective programs of local translation.

Accumulated evidence supports a role for extracellular cues in modulating local mRNA translation to control nociceptor excitability and the generation of hyperalgesia (Khoutorsky & Price, 2018; Price & Inyang, 2015). Extracellular signaling through kinase cascades is one means of rapidly exerting post-transcriptional control of gene expression in nociceptor processes. For example, mammalian target of rapamycin complex 1 (mTORC1) and extracellular signal-regulated kinases (ERK), two important kinases for rapid translational control, can both be activated through tyrosine receptor kinase (Trk) ligation (e.g., by elevated NGF) or by interleukin 6 (IL-6) stimulation in settings of nociceptor sensitization or hyperalgesic priming (Melemedjian et al., 2010, 2014; Topisirovic & Sonenberg, 2011); hyperalgesic priming involves plasticity in pain pathways which allows a prior exposure or injury to result in elevated pain sensitivity to subsequent stimuli which might otherwise be subthreshold (Kandasamy & Price, 2015). Adenosine monophosphate activated protein kinase (AMPK) activation leads to decreased mTORC1 and ERK signaling, and reduced pathological hyperalgesia (Melemedjian et al., 2011; Price et al., 2016; Price & Dussor, 2013; Russe et al., 2013; Tillu et al., 2012). Inhibition of mTORC1 by local administration of rapamycin or treatment with the global protein synthesis inhibitor anisomycin also reduce injury-induced mechanical hypersensitivity and block the development of priming (Jiménez-Díaz et al., 2008; Price et al., 2007). In the aforementioned studies, emphasis was placed on the extracellular cues and kinase cascades through which mTORC1 activation can stimulate translation initiation by phosphorylation of initiation factors such as eukaryotic translation initiation factor 4E-binding protein 1 (4EBP) and eukaryotic initiation factor 4F (eIF_4F). These effects promote efficient mRNA translation and function to enhance bulk protein synthesis. It is worth noting, however, that in other systems, these same kinase cascades (mTORC1 and ERK) have been linked not only to bulk changes in protein synthesis, but also to regulation of the specificity of protein synthesis programs. One underlying mechanism involves the impact of these kinase cascades on microRNA (miRNA) biogenesis and miRNA-mediated repression (Amen et al., 2017; Y.-W. A. Huang et al., 2012; Oldach et al., 2018; Totary-Jain et al., 2013; P. Ye et al., 2015).

Spatiotemporal regulation of translation to impact local proteomes can be achieved at multiple points, through the regulation of miRNA levels and miRNA-mediated repression, control of ribosome recruitment and ribosomal heterogeneity, and modification of the diversity and *cis*-occupancy of 5′ UTRs and 3′UTRs (Biever et al., 2019). 5′UTR diversity can provide alternative translation start sites and initiation rates that promote the production of spatiotemporally varied protein isoforms (Blair et al., 2017; Cheng et al., 2018). 3′UTRs are canonical sites for *cis*-regulatory binding by miRNAs, other ncRNAs, and RNA binding proteins (RBPs) which can impact mRNA stability, localization, and translation (Tushev et al., 2018). Varying the length of 3′UTRs may generate different binding sites for miRNAs and RBPs, which expands the potential for differential translational regulation of otherwise identical mRNA species (Elkon et al., 2013; Miura et al., 2014; Tushev et al., 2018). Both miRNAs and RBPs may, albeit less commonly, regulate target mRNA translation through binding to other regions of the transcript, including the 5′UTR and protein coding regions. Of these

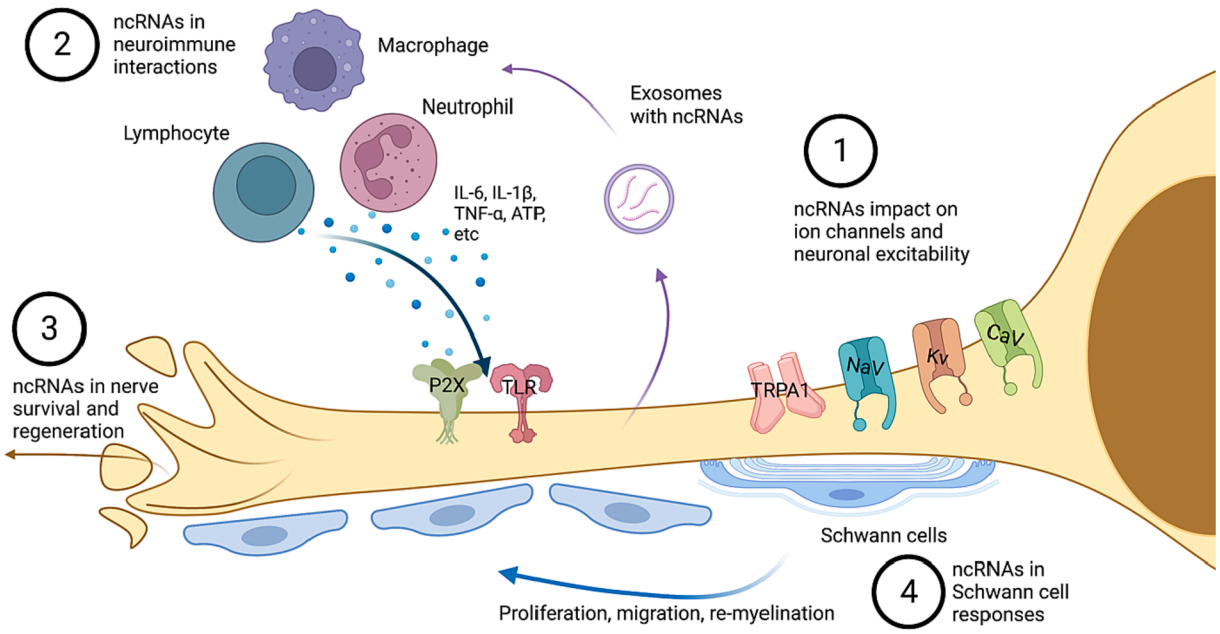

Fig. 1. Non-coding RNAs (ncRNAs) and the participants in their local regulation of plasticity in the peripheral nervous system. Regulatory pathways and mechanisms of ncRNAs in nociceptive plasticity and persistent pain as discussed in this review are highlighted in numbers 1–4. ncRNAs are altered in response to nerve injury and involved in regulation of neuronal excitability (1), neuroimmune interactions (2), neuronal survival and axon regeneration (3), Schwann cell dedifferentiation and proliferation (4), as well as intercellular communication.

potential translation regulatory mechanisms which might be used to regulate protein synthesis in the generation of persistent pain following nerve injury, the most compelling evidence to date has implicated ncRNAs.

ncRNAs in translational regulation of neuronal plasticity

ncRNAs are transcripts that do not have protein-coding potential. 98 % of the mammalian genome is transcribed into ncRNAs rather than protein-coding mRNAs, and ncRNAs are integral to regulating protein expression (Earls et al., 2014; Weiss et al., 2015). ncRNAs, and miRNAs in particular, have been found to be pervasive within dendrites and synapses of the CNS and to participate in neuronal plasticity, including during learning and memory (Lugli et al., 2008, 2012; Smalheiser, 2014). More recently, ncRNAs have also been appreciated to play vital roles in regulating the biological behaviors of neurons and Schwann cells after peripheral nerve injury, including neuronal survival and nerve regeneration, Schwann cell dedifferentiation and proliferation, and neuroimmune responses (Ghibaudi et al., 2017; M. Liu et al., 2022; Tang & Sun, 2020; Yu et al., 2015).

ncRNAs are classified based on their biogenesis, size, and functions. Long non-coding RNAs (lncRNAs, > 200 nt) regulate gene expression at multiple levels including chromatin modulation, transcription interference, mRNA stabilization and depletion, alternative splicing, and in some cases by acting as miRNA 'sponges' to buffer cellular miRNA levels. lncRNAs that function as miRNA sponges contain multiple copies of binding elements for specific miRNA and are located in the cytoplasm, while other lncRNAs are in the nucleus (Bridges et al., 2021; Statello et al., 2021; Thomson & Dinger, 2016). Circular RNAs (circRNAs, variable length, 200–2000 nt) are transcribed from exons and can contain miRNA binding site elements, some of which are proposed to exert highly stable and specific miRNA sponging effects in the cytoplasm to regulate miRNA abundance and target repression (T. B. Hansen et al., 2013; Hentze & Preiss, 2013; Memczak et al., 2013). Competitive binding of specific miRNAs away from other mRNA targets is believed to allow some circRNAs and lncRNAs to interact with programs of transcript repression by miRNAs and to impact specific targets in gene expression. Other types of short ncRNAs including Piwi-interacting RNAs (piRNAs) or transfer RNA (tRNA) fragments, have not yet been sufficiently studied in the PNS, and are therefore not discussed in this review.

miRNAs are the most well-studied small ncRNAs in the nervous system. The majority of mature miRNAs (~22nt) are produced by sequential processing of precursor RNAs. miRNAs are initially produced in the nucleus by RNA polymerase II as primary miRNAs (pri-miRNAs), which are then cleaved by nuclear Drosha to produce precursor miRNAs (pre-miRNAs). Pre-miRNAs are exported to the cytoplasm and processed by the RNase III endonuclease Dicer to generate mature miRNAs. One strand of the mature miRNA duplex can be loaded onto members of the Argonaute (Ago) family of proteins to participate in the RNA-protein complex known as the RNA-induced silencing complex (RISC) (Czech & Hannon, 2011; O'Brien et al., 2018). miRNAs in the RISC bind to partially complementary sites, typically in 3′UTRs, of their target mRNAs to induce translational repression and mRNA degradation (Iwakawa & Tomari, 2022; Kalpachidou et al., 2020). Effective target binding by miRNAs is often dominated by base-pairing with the target in a miRNA region termed the 'seed' sequence, positions 2–7 from the miRNA 5′ end. Note that miRNA precursors have two strands: miR-5p and miR-3p. While miRNA 5p/3p are often concordantly expressed and both arms can be functional, one arm can predominate in levels and function in different cell type, development, or stimulus contexts. In this review, we will assume the miRNA to be 5p and denote if the 3p was specifically implicated in a given effect. Both pre-miRNAs and Dicer (as well as mature miRNAs) are found in neuronal processes, including the processes of peripheral neurons, and pre-miRNAs can be efficiently cleaved into mature miRNA locally at synapses in a manner responsive to external signals (Kim et al., 2015; Lugli et al., 2005, 2008; D. Wu & Murashov, 2013). Further, a pre-miRNA like reporter of miRNA maturation has been used to show that Dicer may function in a spatially restricted manner to yield compartment-specific activity-dependent production of miRNAs and miRNA-mediated repression in dendrites of CNS-derived neurons (Sambandan et al., 2017). This local regulatory feature is likely to also exist in axons of peripheral neurons, although it has not yet been demonstrated.

Cellular machinery regulating the processing, abundance, and function of ncRNAs, especially miRNAs, has been shown to function in many forms of neuronal plasticity and is central to generating enduring physiological changes following nerve injury. Proteins involved in the regulation of miRNA biogenesis and RISC-mediated repression are present in the distal axons of sensory neurons and are regulated in an injury-responsive pattern (Kim et al., 2015; Murashov et al., 2007; D. Wu et al., 2011; D. Wu & Murashov, 2013). The RISC components Ago2 and the Fragile X Mental Retardation Protein (FMRP), for example, are upregulated following nerve injury (D. Wu et al., 2011). Proteins involved in the biogenesis or altered processing of pre-miRNAs, such as Dicer, KH-type splicing regulatory protein (KSRP) and Lin28 homolog A (Lin28a), an RNA binding protein involved in Lethal-7 (let-7) miRNA biogenesis, are also found in the somata and axons of peripheral sensory neurons (Kim et al., 2015; X. Li et al., 2021). In support of localized processing of miRNAs, nerve injury has been shown to lower levels of specific miRNA precursors within axons, consistent with spatiotemporal regulation of translation (Kim et al., 2015). These pathways are discussed in more detail in relevant sections below.

Growing evidence has revealed that ncRNAs play diverse roles in the pathophysiological processes that occur in peripheral tissues after nerve injury (Kalpachidou et al., 2020; Y. Wang et al., 2021; D. Wu et al., 2011). In this review, we discuss local ncRNAs found in the PNS that can specify programs of protein synthesis contributing to nociceptive plasticity and persistent pain. These ncRNAs are involved in neuroimmune interactions, neuronal survival and axon regeneration, Schwann cell dedifferentiation and proliferation, intercellular communication, and the ectopic generation of action potentials in primary afferent processes (Fig. 1). We will also highlight existing commonalities in ncRNA regulation found in other systems that could be informative in interpreting the physiological functions of ncRNAs in the PNS.

ncRNA impact on ion channel and neuronal excitability following nerve injury

Altered ion channel kinetics and membrane excitability following nerve injury contribute to ectopic action potential generation and lowered firing thresholds within nociceptive neurons that in turn promote persistent pain and hyperalgesia. Several lines of evidence have implicated ncRNAs in regulating the dynamics of ion channels and neuronal excitability in nociceptive neurons in the setting of neuropathic pain. In some cases, local functions for this regulation within nerve processes have been established, but in other instances knowledge of spatially compartmentalized roles remains incomplete.

Ubiquitous constitutive loss of Dicer, a critical upstream enzyme promoting the biogenesis of miRNAs, results in early embryonic lethality and has also been shown to specifically impact neural crest development (Bernstein et al., 2003; Zehir et al., 2010). However, selective knockout of Dicer, in nociceptive neurons expressing Nav1.8, has been shown to alleviate neuronal hyperexcitability caused by treatment with inflammatory mediators and to attenuate inflammatory pain (J. Zhao et al., 2010). Nociceptor-enriched mRNA transcripts encoding proteins that regulate excitability, such as sodium channels and receptors (e.g., Nav1.8, P2X purinoceptor 3 (P2X3), RUNX family transcription factor 1 (Runx-1)), were downregulated in the Dicer deficient condition, suggesting a critical role of Dicer in upregulating these hyperexcitability associated transcripts in sensory neurons (J. Zhao et al., 2010). Subsequent work using a ubiquitous but inducible (CAG-CreER / Dicer $^{fl/fl}$) mouse model with knockout of Dicer at 8 weeks of age, demonstrated that the number and size of regenerating sciatic nerve fibers following sciatic nerve crush were lower in the absence of Dicer (D. Wu et al., 2012). This report did not specifically link Dicer to the regulation of particular transcripts contributing to excitability within the injured sciatic nerve, but did demonstrate reduced nerve conduction velocity in isolated sciatic nerve segments and delayed recovery from mechanical hypersensitivity in the Dicer-deficient mice.

Several individual miRNAs have been reported to alter nociceptive excitability by regulating the expression of voltage-gated sodium channels. The SCN9A (Sodium Voltage-Gated Channel Alpha Subunit 9) transcript, which encodes Nav1.7, is targeted by miR-182 and miR-30b (W. Cai et al., 2018; Shao et al., 2016). The downregulation of miR-182 and miR-30b in DRG following spared nerve injury (SNI) was linked to elevated expression of Nav1.7 ion channel alpha subunits in nociceptive neurons and the development of hypersensitivity. Consistent with this idea, administration of either miR-182 or miR-30b agomir (miRNA mimics) could effectively attenuate the SNI induced mechanical hypersensitivity in mice (W. Cai et al., 2018; Shao et al., 2016). A recent study showed that miR-182 regulates the translation of cofilin-1 mRNA locally in the retinal ganglion cell axons of *Xenopus laevis*, indicating that miR-182 has the potential to be involved in the local regulation of mRNA translation in neuronal processes (Bellon et al., 2017). There is also evidence that miR-182, miR-30b-5p, and miR-30b-3p are differentially expressed in the sciatic nerve of rats following sciatic nerve transection, further suggesting that miR-182 and miR-30b might participate in local mRNA translation in neuronal processes (Yu et al., 2011).

The SCN3A (Sodium Voltage-Gate Channel Alpha Subunit 3) transcript, which gives rise to the voltage-gated sodium channel type IX α subunit, Nav1.3, has a 3′UTR targeted by miR-30b, miR-183, miR96, and miR384 (H.-P. Chen et al., 2014; C.-R. Lin et al., 2014; Su et al., 2017; G. Ye et al., 2020). It should be noted that miR-183 and miR-96 are part of the miR-183 miRNA cluster (also containing miR-182); miRNA clusters are miRNAs with adjacent chromosomal locations which are transcribed together. Following peripheral nerve injury, these miRNAs are downregulated in DRG, with miR-30b and miR-384 also reported to be downregulated in the spinal cord. Downregulation of these miRNAs was shown to elevate Nav1.3 mRNA and protein levels in sensory neurons and to contribute to hyperexcitability. Administration of their agomirs was reported to suppress Nav1.3 expression and attenuate thermal and mechanical allodynia or hyperalgesia (H.-P. Chen et al., 2014; C.-R. Lin et al., 2014; Su et al., 2017; G. Ye et al., 2020). Of note, miR-183 in the DRG has also been shown to regulate the protein synthesis of brain derived neurotrophic factor (BDNF), which is well-known for its prominent roles in modulating neuronal plasticity and inflammatory pathways that are involved in nociceptive adaptive responses (Ji et al., 2009; H. Li et al., 2015). miR-384 also participates in suppression of neuroinflammatory responses relevant to nociception (discussed below) in the DRG and spinal cord by downregulating inflammatory cytokines including IL-6, IL1β, cyclooxygenase-2 (COX-2), and tumor necrosis factor α (TNF-α) (Y. Chen et al., 2018; Z.-J. Zhang et al., 2017). miR-183, miR-96, and miR-384-5p are reported to be differentially expressed within the sciatic nerve of rats following sciatic nerve transection, indicating that these miRNAs could also be involved in regulating local mRNA translation in the neuronal processes (Yu et al., 2011).

miR-7a and miR-34a target the SCN2B (Sodium Voltage-Gated Channel Beta Subunit 2) transcript, which produces the sodium channel β2 subunit involved in trafficking and promoting cell surface expression of voltage gated sodium channel α subunits (Brandenburger et al., 2019; Sakai et al., 2013). Levels of miR-7a and miR-34a were found to decrease in DRG following spinal nerve ligation (SNL) and chronic constriction injury (CCI) respectively, leading to the upregulation of β2 subunit expression and elevated sodium channel cell surface insertion. Physiological relevance to the development of persistent pain was established by adeno-associated virus (AAV) mediated expression of a miR-7a antagomir (miRNA inhibitor) in the DRG which increased SCN2B expression and led to mechanical and thermal allodynia in naïve rats (Sakai et al., 2013). miR-34a also targets the transcript encoding vesicle-associated membrane protein 2 (VAMP-2), which is known to be upregulated following nerve injury by CCI (Brandenburger et al., 2019). VAMP-2 functions critically in regulated exocytosis, and is well-studied for its roles in neurotransmitter release and synaptic plasticity (Madrigal et al., 2019; Rizo & Südhof, 2012). VAMP-2 has also been implicated in

the initiation of inflammatory pain through increases in the synaptic vesicle membrane protein synaptophysin (H.-H. Zhang et al., 2012). While there is evidence that miR-7a is differentially expressed in the sciatic nerve of rats following sciatic nerve transection, suggesting possible regulation of local mRNA translation, further investigation is needed to elucidate whether miR-34a could participate in regulating transcripts in neuronal processes (Yu et al., 2011).

miRNAs are often arrayed in polycistronic clusters in the genome. The miR-17/92 cluster (miR-17, miR-18a, miR-19a, miR-20a, and miR-82a) is highly conserved with well-supported roles in development and oncogenesis (Mogilyansky & Rigoutsos, 2013). Members of the miR-17/92 family, and the associated primary miRNA precursor transcripts, were found to be persistently upregulated in the DRG in studies using the SNL model of neuropathic pain (Sakai et al., 2017). In this context, the mir-17/92 miRNAs were found to repress the expression of voltage-gated potassium channels, including Kv1.1, Kv1.4 and Kv4.3, resulting in decreased potassium currents in nociceptive neurons, contributing to hyperexcitability and the development of pain (Sakai et al., 2017). Blockade of members of the miR-17/92 cluster with tough decoy (TuD) antisense RNAs prevented mechanical allodynia and could reverse the established allodynia (Sakai et al., 2017). The miR-17/92 cluster has also been reported to affect axonal outgrowth in embryonic cortical neurons through the local regulation of PTEN protein expression, indicating that the miR-17/92 cluster could impact local mRNA translation in axons (Y. Zhang et al., 2013). Additionally, members of the miR-17/92 cluster, including miR-17-3p, miR-18a, and miR-20a, have been found to be differentially expressed in the sciatic nerve of rats following sciatic nerve transection, further suggesting that they could be involved in local mRNA translation (Yu et al., 2011).

Integrative regulation of multiple transcripts in a given process or pathway is a common feature of miRNA-mediated control. The targeting and repression of all three Cav1.2 subunits (Cacna1c, Cacna2d1, and Cacnb1) by miR-103 is an example of this type of regulation in the context of persistent pain (Favereaux et al., 2011). Overexpression or knockdown, respectively, of miR-103 in cultured spinal cord neurons had reciprocal effects of decreasing or increasing levels of the Cav1.2 calcium channel subunits and recorded calcium channel transients. Activation of Cav1.2 in dorsal horn spinal cord neurons plays important roles in long-term sensitization and upregulation of Cav1.2 has been proposed as a key mechanism in persistent neuropathic pain. (Fossat et al., 2010). In the SNL model, decreased miR-103 levels were observed in spinal cord dorsal horn neuronal somata and processes ipsilateral to the injury with correspondingly increased Cav1.2 subunits (Favereaux et al., 2011). Intrathecal administration of miR-103, but not a seed-mutated control, reduced expression of all three Cav1.2 subunits, which alleviated both mechanical and cold hypersensitivity in the rat SNL model (Favereaux et al., 2011). Interestingly, this robust regulatory loop has also been reported to govern calcium signaling by Cav1.2 in non-neuronal cell types (Sun et al., 2015). miR-103 has been found to be differentially expressed in the rat sciatic nerve following sciatic nerve transection, indicating that miR-103 has the proximity for potential involvement in local regulation of mRNA translation (Yu et al., 2011).

Emerging evidence suggests that lncRNAs are also dysregulated following nerve injury and play pivotal roles in modulating ion channels and neuronal excitability. Kcna2 encodes potassium voltage-gated channel subfamily A member 2. The lncRNA KCNA2-AS (Kcna2 antisense RNA) is upregulated in the DRG following peripheral nerve injury through activation of myeloid zinc finger protein 1 (MZF1), a transcription factor that binds to the Kcna2-AS promoter (X. Zhao et al., 2013). KCNA2-AS has been shown to selectively target the Kcna2 transcript, leading to a reduction in both the transcript and Kcna2 protein. Administration of KCNA2-AS reduced K+ current and depolarized DRG neuronal resting membrane potential with increased neuronal excitability, which in turn promoted mechanical and cold hypersensitivity in vivo. The KCNA2-AS lncRNA has also been demonstrated to regulate cellular excitability in a variety of other settings including cardiac arrhythmia (Long et al., 2017). While Kcna2 is predominantly expressed in axons and presynaptic terminals, further investigation is needed to elucidate whether KCNA2-AS is present in neuronal processes where it might participate in local regulation of mRNA translation.

An unconventional extracellular role for a miRNA in nociceptor regulation, involving the binding and modulation of receptor-ion channel coupling, has also been reported. Let7b, a member of the let-7 family of miRNAs, was reported to be released from DRG neurons and to subsequently induce rapid inward currents and action potentials in sensory neurons through the activation of toll-like receptor-7 (TLR7) and its coupling to the transient receptor potential ankyrin 1 (TRPA1) ion channel (Park et al., 2014, p. 1). These responses required the GU-rich core (GUUGUGU) motif, occurred only in neurons co-expressing TLR7 and TRPA1, and were abolished in mice lacking TLR7 and TRPA1. Several controls, including the surface co-localization of fluorescently labeled let-7b, TLR7, and TRPA1, as well as inside-out patch electrode recordings, were used to support the authors' conclusion that hyperexcitation by let-7b occurred due to extracellular actions. Additionally, plantar delivery of let-7b was shown to elicit persistent TLR7/TRPA1 dependent mechanical allodynia, while inhibiting let7b could reduce pain (Park et al., 2014, p. 1). In addition to other let-7 family members, let-7b is differentially expressed in the rat sciatic nerve following sciatic nerve transection, suggesting that let-7b could be involved in local mRNA translation in neuronal processes (von Schack et al., 2011; Yu et al., 2011).

ncRNAs in neuroimmune interactions following nerve injury

Neuroimmune interactions play significant roles in the development of neuropathic pain following nerve injury. Immediately following injury, neutrophils and resident macrophages, followed by circulating macrophages, invade the injury site and begin to release pro-inflammatory cytokines and to phagocytose fragments of degenerating axons in a process termed Wallerian degeneration that is correlated with neuropathic pain development (Myers et al., 2006; Thacker et al., 2007). The upregulation of released pro-inflammatory cytokines, including TNF-α and IL-6, drives neuroinflammation and can induce action potential generation in peripheral nociceptors. Lymphocytes including T lymphocytes may extravasate into the DRG, and the cytokine profiles of Type I (pro-inflammatory) and Type II (anti-inflammatory) helper (CD4+) T cells are associated with increases and decreases in pain, respectively (Thacker et al., 2007). Interruption of immune cell activation, downregulation of proinflammatory cytokines, or inhibition of neuronal responses to neuroinflammation are important for modifying the development and persistence of neuropathic pain, and these processes are modulated by miRNAs through their downregulation of specific mRNA targets in inflammatory pathways.

The mammalian target of rapamycin (mTOR) / Akt serine threonine kinase (AKT) pathway has been implicated in the development of neuroinflammation and neuropathic pain, in part, due to its role in activation of immune cells and macro-autophagy (Shi et al., 2018). Targeting and downregulation of serine/threonine kinase 3 (AKT3) by miR-145, miR-15a, and miR-20b has been observed to decrease mechanical allodynia and thermal hyperalgesia post-injury through the reduction of mTOR signaling and consequent disinhibition of autophagy and decreased pro-inflammatory cytokine expression (L. Cai et al., 2020; Shi et al., 2018; You et al., 2019). miR-15 family member miR-15b, unlike miR-15a, may have a pro-inflammatory effect following nerve injury as miR-15b targets the aspartyl protease β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) for repression (Ito et al., 2017). BACE1 is known to regulate pro-inflammatory cytokine receptor tumor necrosis factor receptor 1 (TNFR1), with lowered BACE1 levels resulting in elevated TNFR1 (L. Liu et al., 2016; Vassar et al., 2014). Mice deficient in BACE1 exhibited elevated TNFR1 and downstream signaling in injured peripheral nerves, with elevated influx of macrophages to the injured nerves (L. Liu et al., 2016); in summary, miR-15b induction

repressed BACE1 to promote inflammation. A pro-inflammatory role for miR-15b has also been reported in a distinct context of viral infection of the nervous system (B. Zhu et al., 2016). Although miR-20b was not reported in axons, its family member miR-20a, sharing a seed sequence, as well as miR-15b are amongst a subset of miRNAs identified as enriched in distal axons, relative to neuronal cell bodies; these findings place the miRNAs in a position to mediate local regulation of translation although this function remains to be investigated. (Natera-Naranjo et al., 2010).

P2X purinoreceptors mediate responses to ATP, which can be released from damaged cells, and play central roles in coupling cell and tissue damage to cytokine release and inflammatory responses. Multiple subtypes of the P2X purinoreceptors participate in inflammatory pain following nerve injury and are also targets of regulation by miRNAs. P2X purinoreceptors function as ligand-gated ion channels and transduce ATP-evoked nociceptor activation. Sensitization of P2X purinoreceptors and transient receptor potential vanilloid 1 (TRPV1) ion channels has been implicated by multiple studies in the development of chronic inflammatory pain and peripheral neuropathy (Brederson et al., 2013; Chiba et al., 2017; Kaneko & Szallasi, 2014; Kuan & Shyu, 2016). The $P2X_3$ subtype, in particular, is abundantly expressed in DRG neurons including within processes and is proposed to function in retrograde signaling from activation within processes to the DRG soma (X.-Q. Chen et al., 2012). $P2X_3$ expression can be modulated by the lncRNA MRAK009713, which was shown to be upregulated following peripheral nerve injury using a CCI model (G. Li et al., 2017)., Overexpression of MRAK009713 increased $P2X_3$ expression and function, promoting mechanical and thermal allodynia (G. Li et al., 2017). MRAK009713 was predicted to interact with the $P2X_3$ receptor, and this *in-silico* prediction was validated in heterologous cells using an RNA immunoprecipitation approach. Administration of MRAK009713 siRNA suppressed $P2X_3$ expression and alleviated hyperalgesia (G. Li et al., 2017), although spatial localization of these effects to DRG neuronal processes was not examined.

Several toll-like receptors (TLR) are involved in neuroimmune responses and thought to participate in the etiology of persistent pain. TLRs 7 and 8 localize predominantly in intracellular compartments and recognize single-stranded nucleic acid based ligands, including miRNAs (Bayraktar et al., 2019). The expression of TLR8, which detects viral single-stranded RNA (ssRNA) as part of the innate immune system, was observed to be upregulated in the DRG following SNL injury (Z.-J. Zhang et al., 2018). In earlier studies, both miR-21 and miR-29a had been reported to bind as ligands to TLR8 in immune cells (Fabbri et al., 2012). Accordingly, the authors tested whether miR-21, which was also observed to increase robustly in neurons following injury, could activate TLR8. Delivery of miR-21 mimics activated TLR8 by readouts of elevated phospho-ERK in the mitogen-activated protein kinase (MAPK) pathway, elevated inflammatory mediators, and neuronal excitability (Z.-J. Zhang et al., 2018). miR-21 mimics induced neuropathic pain in control but not Tlr8-/- mice, while inhibitors of miR-21 could alleviate neuropathic pain. Knockdown of miR-21 by siRNA was observed to alleviate pain (Z.-J. Zhang et al., 2018). The relevant source of upregulated miR-21 in this SNL injury setting, as well as the potential sequences required for miR-21 binding to TLR8 remain to be determined, though colocalization of TLR8 and miR-21 in DRG neurons was supported by in-situ hybridization with immunostaining (Z.-J. Zhang et al., 2018). These authors did not further evaluate the spatial localization of miR-21 in their SNL injury model, however a separate survey study reported that miR-21 is upregulated in sciatic nerve tissue following nerve injury, indicating potential for a local regulatory role by miR-21 (Yu et al., 2011). In addition, overexpression of miR-21 has been demonstrated to impact both overall as well as intra-axonal protein synthesis in cultured DRGs (Kar et al., 2021). It is worth noting that while miRNA binding to receptors is not common, this noncanonical regulatory role for miRNAs has been previously reported. Let-7b binding to TLR7 in the modulation of spontaneous pain and miR-711 binding to TRPA1 in itch responses are examples of this unconventional role for miRNAs in sensory systems (Q. Han et al., 2018; Park et al., 2014).

In recent years, high-throughput transcriptomics has led to documentation of numerous circRNAs, many of whose functions remain obscure. circRNAs are highly stable ncRNAs produced through non-canonical intron backsplicing to covalently link the 5′ and 3′ ends. Like lncRNAs, circRNAs have been proposed to act as miRNA sponges through the competitive binding of specific sequence corresponding miRNAs away from target mRNAs. Whether or not a given circRNA has a physiologically meaningful impact on miRNA levels can depend upon the expression levels of both the circRNA and the miRNA. The homeodomain-interacting protein kinase 3 circRNA (circHIPK3), is encoded within exon 2 of the homeodomain-interacting protein kinase 3 (hipk3) gene and has been previously characterized as a highly expressed miRNA sponge with roles in settings of cancer and neuropathic pain (L. Wang et al., 2018; Y. Zhang et al., 2020). CircHIPK3, like other circRNAs, has been found to sponge several distinct miRNAs for which it contains multiple binding sites, including miR-124 (Zheng et al., 2016). In a rat model of diabetic neuropathic pain, circHIPK3 was found to be upregulated in the DRG and was also abundant in the serum from diabetic patients suffering from pain (L. Wang et al., 2018). CircHIPK3 was found to sponge miR-124, as verified by RNA pull-down and luciferase assays, which led to de-repression of pro-inflammatory cytokine transcripts (L. Wang et al., 2018). Knockdown of circHIPK3 was sufficient to alleviate mechanical allodynia and thermal hypersensitivity (L. Wang et al., 2018), and a reversal of this effect by expression of a miR-124 inhibitor provided evidence to support a miR-124 sponging mechanism in circHIPK3 function. These results imply that miR-124 inhibits pro-inflammatory pathways and that buffering of miR-124 by the competing endogenous RNA (ceRNA) action of circHIPK3 can lead to upregulated translation of pro-inflammatory transcripts. However, miR-124 may not directly target pro-inflammatory transcripts for repression, and in other settings of neuroinflammation miR-124 has been shown to promote microglial activation through targeting components of the MAPK and nuclear factor kappa B (NF-κB) pathway (C. Yang et al., 2022; L. Yao et al., 2019). The downregulation of miR-124 within the sciatic nerve following nerve injury also indicates a potential dynamic interaction of circHIPK3/miR-124 locally near the injury sites for neuroinflammatory responses although circHIPK3 expression has not been demonstrated within the sciatic nerve, to our knowledge (Yu et al., 2011). CCI of the rat sciatic nerve was shown to induce circHIPK3 expression in the dorsal horn of the spinal cord.

miRNAs can exist extracellularly in either exosomal or non-exosomal forms. Exosomes are secreted vesicles that can shuttle their cargo, which can include ncRNAs, mRNAs, DNA, lipids, and proteins, to recipient cells. Exosomal transport of miRNAs from neurons to target cells has been reported to have impacts on pain and may play a particular role in the signaling between neurons and cells of the immune system. Following nerve trauma by SNI, miR-21 was found to be elevated in DRG sensory neuron cell bodies (Simeoli et al., 2017). Using DRG neuronal cultures, the authors found that capsaicin-mediated TRPV1 activation could also elevate miR-21 levels and that extracellular vesicles (EVs) containing miR-21 were released from DRG sensory neurons and phagocytosed by macrophage recipient cells (Simeoli et al., 2017). Intracellular miR-21 levels increased in macrophages following uptake of EVs containing miR-21, which was linked to increased extracellular pro-inflammatory cytokine abundance, and an elevated activated (M1-like) macrophage phenotype. Conditional deletion of miR-21 in the DRG sensory neurons was able to reduce both hyperalgesia following SNI as well as inflammatory macrophage recruitment to the DRG. miR-21 has also been suggested to function as an endogenous ligand for the TLR8 in the TLR8+ neurons of the DRG and to promote neuropathic pain induced by SNL (Z.-J. Zhang et al., 2018).

Intercellular signaling by neuronal exosomal miRNAs has also been observed in other settings of chronic pain. Direct targeting of IL-6 by exosomal miR-338 was reported to play a role in complex regional pain

syndrome (CRPS), a chronic pain disorder featuring persistent inflammation (Ramanathan et al., 2019). In a case study, CRPS patients with lower plasma exosomal levels of miR-338 responded less well to treatment by plasma exchange, and overexpression of miR-338 in a monocytic cell lines induced by lipopolysaccharide rescued changes in pro-inflammatory cytokine expression (Ramanathan et al., 2019). Targeting of the predicted IL-6 3′UTR by miR-338 was confirmed by luciferase assay in which overexpression of miR-338 reduced activity of the IL-6 reporter, although a miR-338 antagomir did not alter basal IL-6 reporter levels. These findings were well-replicated in observations of miR-338 impacting endogenous IL-6 transcripts in the monocyte cell lines (Ramanathan et al., 2019). Interestingly, local delivery of miR-338 in injured sciatic nerve has been found to improve neuromuscular activity by inhibiting Schwann cell inflammatory effects, indicating an anti-inflammatory role of miR-338 locally in the injured nerves (Xiaojing et al., 2021).

ncRNAs in nerve survival and regeneration following nerve injury

The development of persistent pain following nerve injury typically occurs concomitantly with failed nerve regeneration. Injury-induced changes in peripheral nerve gene regulatory cascades not only induce pathophysiological neuropathic pain but can also participate in nerve regeneration. During effective nerve regeneration, changes in axonal protein expression shift the physiology of neurons toward survival and regeneration. The molecular and cellular events involved in the induction and maintenance of neuropathic pain, such as gene programs controlling growth and excitability, can also be shared pathways responsible for producing a microenvironment that stimulates axonal regeneration.

The role of ncRNAs in this relationship can be exemplified by phenotypes associated with loss of Dicer, an upstream positive regulator of miRNA production. Nociceptive neuron-specific loss of Dicer impaired the development of hyperexcitability as discussed above (J. Zhao et al., 2010), while a global inducible loss of Dicer (using a ubiquitous promoter to drive conditional loss of Dicer in a Dicer $^{fl/fl}$ mouse) also exhibited an anti-excitability effect with inhibition of the recovery of evoked action potentials and nerve conduction velocity following nerve injury (D. Wu et al., 2012), as discussed earlier. These Dicer deficiency models differed in the cell-type selectivity (neuron-selective compared to global) and developmental timing of Dicer loss (D. Wu et al., 2012; J. Zhao et al., 2010). Both publications implicated small RNAs, most of which require Dicer for their production, as essential for the maintenance of normal levels of transcripts required to alter peripheral pain thresholds. Interestingly, the global loss of Dicer was also shown to inhibit nerve regeneration (D. Wu et al., 2012). Inducible Dicer-deficiency impaired nerve structural and functional regeneration following sciatic nerve injury, and prevented axon outgrowth in cultured DRG neurons, extending the importance of Dicer to successful functional recovery following nerve injury. The phenotypes of lowered excitability and impaired nerve regeneration could be expected to have opposing effects on the development of persistent pain. However, it is not uncommon that the same gene programs governed by miRNAs could function to promote growth/survival/regeneration pathways as well as to induce neuronal firing. The collective impact of such miRNA-governed programs on persistent pain could depend upon the cell type affected, as well as whether full nerve recovery is feasible following injury.

The regulation of individual miRNAs can also participate in the promotion of neuronal outgrowth and axon regeneration following nerve injury, as well as modulating persistent pain. The miR-133b miRNA has been linked to both promotion of neuron growth and regeneration as well as regulation of persistent pain. Early work first implicated miR-133b in the tissue regeneration of injured skeletal muscle (Nakasa et al., 2010). Subsequently, miR-133b was also demonstrated to promote functional recovery and axon regeneration in injured neurons within the Zebrafish brainstem following spinal cord transection (Ym et al., 2011). In this context, miR-133b was upregulated in the nucleus of the medial longitudinal fascicle (NMLF) and was reported to contribute to successful axon regeneration by targeting small GTPase Ras homolog family member A (RhoA), an inhibitor of neurite outgrowth-related molecules (Ym et al., 2011). Several studies from independent laboratories have demonstrated that RhoA is upregulated following spinal cord injury and inhibits functional recovery, and that strategies to inhibit RhoA activity can facilitate repair and functional recovery (Conrad et al., 2005; Dergham et al., 2002; Dubreuil et al., 2003; Ellezam et al., 2002; Erschbamer et al., 2005; Fournier et al., 2003). Consistent with these findings, upregulation of miR-133b in NMLF facilitated proper regeneration by inhibiting RhoA production (Ym et al., 2011). RhoA mRNA has been shown to be present in DRG axons and is translated locally at axon growth cones to regulate neuronal growth, suggesting that miR-133b could be involved in local RhoA translation in neuronal processes (K. Y. Wu et al., 2005). Additionally, it has been shown that miR-133b is differentially expressed in the rat sciatic nerve following sciatic nerve transection, further suggesting that miR-133b could be involved in local mRNA translation in neuronal processes (Yu et al., 2011). Upregulation of miR-133b-3p, a member of the miR-133b family, has also been found to be correlated with decreased neuropathic pain in rats after peripheral nerve injury (Norcini et al., 2018). Overexpression of miR-133-3b-3p via lentiviral vectors after nerve injury reduced symptoms of mechanical and cold allodynia in rats, suggesting that miR-133b-3p is protective against neuropathic pain, although the mechanism for this effect and its relation to the pro-growth response produced by miR-133b has not yet been elucidated (Norcini et al., 2018).

miR-132 has been well-studied for its roles in promoting dendrite complexity, dendritic spine development, and synaptic plasticity (Edbauer et al., 2010; Klein et al., 2007; Magill et al., 2010; Mellios et al., 2011; Mendoza-Viveros et al., 2017; Tognini et al., 2011). Aberrant miR-132 expression or regulation has been linked to major neurodevelopmental, psychiatric, and neurodegenerative diseases. Intriguingly, miR-132 has also been shown to promote neurite growth through its local enrichment in developing axons (Hancock et al., 2014). miR-132 was detected in a screen, carried out in DRG sensory neurons, for miRNAs preferentially enriched in developing axons. Using gain and loss of function experiments, miR-132 was found to promote axon extension by targeting Ras GTPase activator Rasa1 (RASA1) locally within axons (Hancock et al., 2014). RASA1 participates in cytoskeletal regulation and is thought to play a role in responding to axon guidance cues (Dail et al., 2006; Elowe et al., 2001; Holland et al., 1997). In DRG cultures, a system of severed axons was used to demonstrate that miR-132 could locally regulate RASA1 levels (Endo & Yamashita, 2009; Hancock et al., 2014). These findings suggest that miR-132 might be able to contribute to responses requiring sensory neuron axon growth or regeneration by locally governing RASA1 translation; an area which could merit future investigation. Not surprisingly, a role for miR-132 in nociceptive responses following nerve injury has also been investigated. miR-132-3p is significantly elevated in sural nerve biopsies sampled from patients with peripheral neuropathy as compared to healthy controls (Leinders et al., 2016). miR-132-3p has also been observed to be upregulated in rats following SNI, and intrathecal administration of a miR-132-3p antagonist in rats effectively reduced mechanical and heat hyperalgesia, while administration of a miR-132-3p mimic induced pain behaviors in naïve rats. This study suggests that miR-132-3p upregulation can promote neuropathic pain development, although the molecular targets responsible for this and the relationship to miR-132′s pro-growth roles require further investigation (Leinders et al., 2016). miR-132 expression can be regulated by activation of a transcription factor, cyclic AMP response element-binding protein (CREB), known for its prominent role in neuronal plasticity. Prior work has shown that CREB induction of miR-132 can participate in homeostatic downregulation of

methyl-CpG binding protein 2 (MeCP2) (R. Zhang et al., 2015). This regulatory loop of miR-132 has also been implicated in the development of chronic pain following nerve injury, with decreased levels of miR-132 following spared nerve injury reported to impact mechanical hyperalgesia through de-repression of MeCP2 (R. Zhang et al., 2015).

While some miRNAs exhibit pro-growth effects, other miRNAs which are also involved in nociceptive pain have been shown to inhibit neurite growth and to be downregulated following nerve injury. miR-138 has been found to inhibit axon growth *in vitro* and is downregulated in mouse DRG neurons after sciatic nerve injury (C.-M. Liu et al., 2013). miR-138 binds to and represses the transcript for SIRT1, a histone deacetylase that when upregulated is thought to increase the regenerative capacity of neurons (Araki et al., 2004). Histone acetylation classically increases transcription (although the reverse effect can occur), through providing binding sites for bromodomain containing proteins and by decreasing electrostatic interactions between histones and DNA, which collectively render chromosomes more accessible for transcription. Conversely, histone deacetylation classically leads to more compacted chromatin and decreased transcription. SIRT1 is reported to inhibit miR-138 expression, possibly by binding to regulatory sequences upstream of the pri-miR-138 gene, indicating that miR-138 and SIRT1 are part of a mutual negative feedback loop that regulates axon growth and regeneration (C.-M. Liu et al., 2013). Targeting of SIRT1 by miR-138 is also conserved in human primary keratinocytes, where it is reported to regulate cell senescence (di Val et al., 2012). This finding is consistent with miR-138 upregulation in a spinal cord injury model (J. Chen & Qin, 2020, p. 1), where miR-138 was found to repress SIRT1 leading to modulation of inflammatory responses and the balance of cell survival and apoptosis (J. Chen & Qin, 2020, p. 1). miR-138 has also been linked to alleviation of persistent pain. One study found that intrathecal injection of miR-138 in mice reduced mechanical allodynia and thermal hyperalgesia as well as inflammatory markers in response to SNI (B. Zhu et al., 2019). While employing solely an overexpression approach, this study nonetheless provides another example in which a miRNA, miR-138, previously linked to regulation of axon outgrowth, is also reported to exert a protective effect against nociceptive pain (B. Zhu et al., 2019). Not surprisingly, miR-138 has also been found to locally regulate dendritic spine morphology through action at synaptic sites in hippocampal neurons and is also downregulated in injured sciatic nerve following injury, suggesting that miR-138 has the capacity to participate in local mRNA translation in neuronal processes (H.-P. Lin et al., 2018; Siegel et al., 2009; Yu et al., 2011). Pathways governing autophagy hold prominent roles in functional recovery from nerve injury and are additional control points by which ncRNAs can regulate both regeneration and chronic pain. Members of the miR-34 family, consisting of miR-34a, b, and c, are widely studied as they are transcriptionally upregulated by the p53 tumor suppressor protein and function as tumor suppressors which can inhibit proliferation, and induce apoptosis and autophagy (He et al., 2007). Dysregulation of autophagy by aberrant miRNA expression can participate in peripheral neuropathy. miR-34c is upregulated in trigeminal ganglion neurons and inhibits autophagy in diabetic corneal neuropathy of diabetic mice by directly targeting autophagy related 4B cysteine peptidase (Atg4B), a key member of autophagy core proteins that mediates autophagic membrane extension, closure, and maturation (Hu et al., 2019). A miR-34c antagomir was shown to accelerate ATG4B expression and wound healing via autophagy in vivo, and to increase neurite growth, corneal nerve regeneration, and neuronal density *in vitro*, suggesting that miR-34c mediated downregulation of Atg4B in diabetes contributes to the development of corneal neuropathy by impairing autophagy (Hu et al., 2019). Additionally, there is evidence that miR-34c is differentially expressed in the rat sciatic nerve following sciatic nerve transection, suggesting that miR-34c could be involved in local mRNA translation in neuronal processes (Yu et al., 2011). miR-34c has also been linked to the reduction of nociceptive pain in several settings, although current literature shows this to occur by pathways distinct from autophagy. miR-34c overexpression was reported to alleviate neuropathic pain symptoms in mice following CCI by inhibiting the nucleotide binding domain-like receptor protein 3 (NLRP3) inflammasome (Xu et al., 2019). In contrast, inhibitors of miR-34c were effective in reducing nociceptive hypersensitivity in both a tumor-associated pain model and a rat CCI model (Gandla et al., 2017; Mo et al., 2020). A number of differences in experimental design, such as the targeted cell type and intervention, timing, and readouts of pain phenotypes may have contributed to the discrepant results observed regarding the directionality of the miR-34c impact on pain.

ncRNAs in Schwann cell responses following nerve injury

After peripheral nerve injury, Schwann cells undergo morphological changes and play essential roles in debris clearance, guidance of axonal outgrowth, and re-myelination of injured or regenerated nerves. ncRNAs modulate key Schwann cell pathways that mediate apoptosis, proliferation, migration, and re-myelination during nerve regeneration. Some of these pathways also directly participate in nociceptive sensitization and persistent pain.

miR-9 is an ancient and well-conserved miRNA which is expressed in both neurons and Schwann cells, and has been implicated in diverse cellular functions including differentiation, proliferation, migration, and tumor formation (Coolen et al., 2013). Elevated levels of miR-9 are reported to inhibit axon regeneration in neurons, with FoxP1 postulated to be the functional target (J. Jiang et al., 2017). Consistently, in Schwann cells, miR-9 inhibits Schwann cell migration and downregulation of miR-9 following nerve injury produces effects which would be expected to promote nerve regeneration (J. Jiang et al., 2017). The downregulation of miR-9 has been shown to increase Schwann cell motility by limiting the deposition of collagen in the extracellular matrix (J. Jiang et al., 2017; X. Wang et al., 2019). miR-9 has also been suggested to impact Schwann cell migration by directly targeting the collagen triple helix repeat containing protein 1 (CTHRC1) for repression; lowered levels of CTHRC1 inhibits the downstream activation of Rac1 GTPase by CTHRC1 (S. Zhou et al., 2014). Rac1 GTPase is a key regulator of cytoskeletal dynamics and cell migration (Pyagay et al., 2005). Downregulation of miR-9 following injury was linked to release of CTHRC1 from repression with consequent enhanced activation of the Rac1 GTPases and elevated Schwann cell motility (S. Zhou et al., 2014). Direct linkage of miR-9, in Schwann cells or otherwise, to pain phenotypes remains understudied. An anti-nociceptive effect from intrathecal administration of miR-9 overexpressing bone marrow mesenchymal stem cells, and consequent reduction in spinal cord neuroinflammatory readouts, has been reported in a mouse model of bone cancer pain (C. Zhu et al., 2020).

The abundant and evolutionarily conserved family of let-7 miRNAs are known to regulate neuronal cell fate and can affect neurodegeneration in the CNS and neuronal regeneration in the PNS (Kucherenko et al., 2012; Lehmann et al., 2012; Zou et al., 2013). Multiple members of the let-7 family have been shown to respond dynamically to nerve injury, although different time courses of response in Schwann cells have been reported (S. Li et al., 2015; Viader et al., 2011; X. Wang et al., 2019). In addition to downregulation of miR-9, let-7 miRNAs are also downregulated in both sciatic nerve in Schwann cells and in DRG neurons following rat sciatic nerve crush injuries (Natera-Naranjo et al., 2010; X. Wang et al., 2019). In this setting let-7 and miR-9 have been found to directly target netrin 1 (Ntn1) and DCC netrin 1 receptor (Dcc) transcripts, respectively (X. Wang et al., 2019), with let-7 and miR-9 overexpression decreasing levels of Ntn1 and Dcc protein in DRG neurons. Let-7 and miR-9 overexpression also impaired neurite growth both *in vitro* and in vivo, suggesting that downregulation of let-7 and miR-9 might promote axon growth and Schwann cell migration through the elevated secretion of Ntn1 and Dcc (X. Wang et al., 2019). The dynamic regulation of Let-7 miRNAs following nerve injury has also been shown to directly modulate expression of nerve growth factor (NGF) in Schwann cells responding to nerve injury (S. Li et al., 2015; S.

Table 1
Ncrnas impact on ion channel and neuronal excitability following nerve injury.

ncRNAs/Biogenesis regulators	Species	Model	Regulation	Location	Target	Physiological functions [1]	Reference
Dicer	Mouse	N/A	Nav1.8 Cre Dicer conditional knockout	Nociceptive neurons	Nav1.8	Inflammatory pain ↓ [2],	(J. Zhao et al., 2010)
miR-182	Rat	Spared nerve injury (SNI)	↓	DRG	Nav1.7 (SCN9A)	Nav1.7 ↑ [3], Mechanical hypersensitivity ↑	(W. Cai et al., 2018)
miR-30b	Rat	SNI	↓	DRG	Nav1.7 (SCN9A)	Nav1.7 ↑, Mechanical hypersensitivity ↑	(Shao et al., 2016)
miR-30b	Rat	Spinal nerve ligation (SNL)	↓	DRG, Spinal cord	Nav1.3 (SCN3A)	Nav1.3 ↑, Mechanical and thermal hypersensitivity ↑	(Su et al., 2017)
miR-183	Rat	SNL	↓	DRG	Nav1.3 (SCN3A) BDNF	Nav1.3 ↑, BDNF ↑, Mechanical hypersensitivity ↑	(Lin et al., 2014)
miR-96	Rat	Chronic constriction injury (CCI)	↓	DRG	Nav1.3 (SCN3A)	Nav1.3 ↑, Mechanical and thermal hypersensitivity ↑	(H.-P. Chen et al., 2014)
miR-384	Rat	CCI	↓	DRG, Spinal cord	Nav1.3 (SCN3A)	Nav1.3 ↑, Mechanical and thermal hypersensitivity ↑, IL-6, IL-1B, COX-2, and TNF-a ↑, Neuroinflammation ↑	(Ye et al., 2020)
miR-7a	Rat	SNL	↓	DRG	SCN2B	SCN2B ↑, Mechanical and thermal hypersensitivity ↑	(Sakai et al., 2013)
miR-34a	Rat	CCI	↓	DRG	SCN2B VAMP-2	VAMP-2 ↑, Mechanical hypersensitivity ↑	(Brandenburger et al., 2019)
miR-7a	Rat	SNL	↓	DRG	NEFL/STAT3 axis	NEFL ↑, STAT3 phosphorylation ↑, Mechanical and thermal hypersensitivity ↑	(Yang et al., 2019)
miR-17/92 cluster (miR-17, miR-18a, miR-19a, miR-20a, and miR-82a)	Rat	SNL	↑	DRG	Voltage-gated potassium channels (KCNA1, KCNA3, KCNA4, KCNA5)	Voltage-gated potassium channels ↓, Outward potassium currents ↓, Mechanical hypersensitivity ↑	(Sakai et al., 2017)
miR-103	Rat	N/A	miR-103 mimic introduction	Spinal cord	Cav1.2	Cav1.2 LTC subunits ↓, Mechanical and cold hypersensitivity ↓	(Favereaux et al., 2011)
Let-7b	Mouse	N/A	↑ in neuronal exosomes by neuronal activation	Exosome released by DRG neurons	TLR7 TRPA1	Inward currents and action potentials ↑, Spontaneous pain ↑	(Park et al., 2014, p. 7)
KCNA2-AS	Rat/ Mouse	SNL	↑	DRG	Kcna2	Kcna2 ↓, Neuronal resting membrane potential ↑, Mechanical and cold hypersensitivity ↑	(X. Zhao et al., 2013) (Long et al., 2017)

[1] Details in manuscript. [2] ↓ Downregulate. [3] ↑ Upregulate.

Yang et al., 2018). Lowered levels of let-7 miRNAs can relieve repression of the targeted NGF transcript, and result in increased NGF secretion by Schwann cells, which in turn enhances axon outgrowth following injury (S. Li et al., 2015). These reports are consistent with evolutionarily conserved roles for the let-7 family of miRNAs in governing transcripts involved in growth and development.

Let-7 family miRNAs are also prominent regulators in the promotion of PNS myelination during neurodevelopment. The Lin28 RNA binding proteins (Lin28a and Lin28b) act post-transcriptionally as negative regulators of let-7 family miRNAs; in the PNS, developmental down-regulation of Lin28b leads to accumulation of let-7 miRNAs (Gökbuget et al., 2015). Notch1 is a well-known negative regulator of myelination, and sustained Notch1 expression is thought to interfere with PNS myelination by opposing expression of early growth response protein 2 (Egr2) (Woodhoo et al., 2009). Let-7 miRNAs can promote myelination by elevating Egr2 expression through direct targeting of the Notch1 3′ UTR and inhibition of Notch signaling (Gökbuget et al., 2015). Lowered levels of let-7 miRNAs, following sustained expression of Lin28b in Schwann cells, were found to inhibit myelination (Gökbuget et al., 2015), which could imply a potential role of let-7 miRNAs in re-myelination following peripheral nerve injury. Another key modulator of let-7 miRNAs, the Lin28a protein, is also upregulated following injury and promotes axon regeneration of both corticospinal axons and the optic nerve, as well as the PNS in adult mice, indicating that Lin28 is critical for regulating growth capacity of multiple cell types (Nathan et al., 2020; X.-W. Wang et al., 2018). In Drosophila nociceptive neurons, upstream regulation of let-7 levels by Lin28 has also been recently shown to govern dendrite arborization in a developmental regulatory circuit (Suzuki et al., 2022). Although a role for let-7 miRNAs in neuropathic pain development requires further exploration, let-7 miRNAs have been reported to be dysregulated in many neuropathic pain models (von Schack et al., 2011; Y. Wang et al., 2021), and modulation

Table 2
Ncrnas in neuroimmune interactions following nerve injury.

ncRNAs/ Biogenesis regulators	Species	Model	Regulation	Location	Target	Physiological functions	Reference
miR-15b	Rat	Chemotherapy-induced chronic neuropathy (CIPN)	↑	DRG	BACE1	BACE1 ↓, Mechanical hypersensitivity ↑	(Ito et al., 2017)
miR-15a	Rat	CCI	↓	Spinal cord	AKT3	AKT3 ↑, IL-6, IL-1β, and TNF-α ↑, Neuroinflammation ↑, Mechanical and thermal hypersensitivity ↑	(L. Cai et al., 2020, p. 15)
miR-145	Rat	CCI	↓	DRG	AKT3/ mTOR axis, AKT3/NF-κB axis	AKT3, NF-κB, mTOR ↑, IL-6, IL-1β, and TNF-α ↑, Neuroinflammation ↑, Mechanical and thermal hypersensitivity ↑	(J. Shi et al., 2018)
miR-20b	Rat	CCI	↓	Spinal cord dorsal horn, Microglia	AKT3	AKT3 ↑, IL-6, IL-1β, and TNF-α ↑, Neuroinflammation ↑, Mechanical and thermal hypersensitivity ↑	(You et al., 2019)
miR-21	Mouse	SNL	↑	DRG	TLR8	TLR8 ↑, Mechanical and thermal hypersensitivity ↑	(Z.-J. Zhang et al., 2018, p. 8)
miR-21	Mouse	SNI	↑ in neuronal extracellular vesicles	Neuronal extracellular vesicles (EVs)	N/A	Macrophage uptake miR-21 containing EVs, Proinflammatory genes (NF-κB p65, iNOS) ↑, Anti-inflammatory genes (CD206, Arginase-1) ↓, M1 macrophage phenotype ↑, Neuroinflammation ↑, Mechanical hypersensitivity ↑	(Simeoli et al., 2017)
miR-338	Human	Complex regional pain syndrome (CRPS) patients	↓ in plasma exchange (PE) poor responders	Exosome	IL-6	IL-6 ↑, Neuroinflammation ↑	(Ramanathan et al., 2019)
circHIPK3	Human	Type 2 diabetes patients	↑	Serum	miR-124	miR-124 ↓,	(L. Wang et al., 2018)
	Rat	(Streptozocin)STZ-induced diabetes	↑	DRG		IL-1b, IL-6, IL-12, TNF-α ↑, Neuroinflammation ↑, Mechanical and thermal hypersensitivity ↑	
MRAK009713	Rat	CCI	↑	DRG	P2X3	P2X3 ↑, Mechanical and thermal hypersensitivity ↑	(G. Li et al., 2017)

of the numerous pro-growth and pro-excitatory mRNA targets of let-7 miRNAs has potential to contribute to neuropathic pain.

Regulation by ncRNAs can also promote Schwann cell proliferation and migration by impacting growth factor levels. The growth factor, BDNF, plays important roles including maintenance of injured neuron survival, promotion of nerve fiber regeneration, and advancement of functional recovery after peripheral nerve injury (Dai et al., 2013). BDNF is produced by both neurons and Schwann cells, and can be secreted by Schwann cells following peripheral nerve injury (Lykissas et al., 2007). BDNF is a target for numerous ncRNAs, including members of the miR-1 family: miR-1, miR-1b, miR-206, and miR-3571. miR-1 was found to be downregulated in sciatic nerve following peripheral nerve injury. miR-1 targets the BDNF transcript in Schwann cells. Consequently, decreased miR-1 following injury leads to upregulation of BDNF transcript, BDNF protein levels, and the secretion of BDNF by Schwann cells (Yi et al., 2016). Elevation or inhibition of miR-1 was shown to reciprocally reduce or enhance SC proliferation and mobility in migration assays. These effects of miR-1 in Schwann cells were attributed to regulation of BDNF based on their abrogation in the context of BDNF knockdown (Yi et al., 2016). The modulation of BDNF expression by miR-1 in DRG sensory neurons and the sciatic nerve is also thought to contribute to hypersensitivity following peripheral nerve damage by CCI, which lowers levels of miR-1 (Neumann et al., 2015). BDNF levels can be regulated through another ncRNA axis involving a lncRNA and a miRNA (lncRNA-miRNA-BDNF). The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA is found to be upregulated in Schwann cells following crush injury of the sciatic nerve (G. Wu et al., 2020). Upregulation of MALAT1 was reported to promote Schwann cell proliferation and migration by sponging miR-129, an action which relieved miR-129-mediated repression of the BDNF transcript and elevated BDNF expression in Schwann cells (G. Wu et al., 2020). miR-129 is not the only miRNA reported to be sponged by MALAT1, which is believed to serve as a ceRNA to sequester several other miRNAs, including miR-101, miR-199, miR-144, miR-154, miR-211, and miR-203 (Q. Zhou et al., 2021). Elevation of MALAT1 following injury has been linked to promoting neuropathic pain by increasing aquaporin 9 (AQP9) expression in spinal cord and microglia through the sponging of miR-154 which targets the AQP9 transcript (J. Wu et al., 2020), indicating a potential role for MALAT1 to regulate hypersensitivity locally in the peripheral nerves, while further investigation is needed.

As discussed in preceding sections, miR-132 has well characterized CNS roles in regulating neurite outgrowth, dendritic spine formation and cognition (K. F. Hansen et al., 2013; Vo et al., 2005; Wayman et al., 2008). miR-132 is also highly expressed in developing axons of DRG sensory neurons and promotes axon extension (Hancock et al., 2014), as well as having reported additional neuronal roles in persistent pain. Following peripheral nerve injury, Schwann cells frequently must

Table 3
Ncrnas in nerve survival and regeneration following nerve injury.

ncRNAs/ Biogenesis regulators	Species	Model	Regulation	Location	Target	Physiological functions	Reference
Dicer	Mouse	Sciatic nerve crush	CAG-Cre^{ER} Dicer conditional knockout	Sciatic nerve, DRG neurons	N/A	Mechanical sensitivity ↓, Nerve anatomical, physiological, and functional recovery ↓, Axon regeneration ↓	(D. Wu et al., 2012)
RISC, P body	Mouse	Sciatic nerve crush	↑	Sciatic nerve, DRG neurons	N/A	RISC components (FMRP, Ago2 and P-100) ↑, P-body components (Dcp1 and GWB IC-6) ↑, (Dcp2 and Ro2) ↓	(D. Wu et al., 2011)
miR-138	Mouse	Sciatic nerve crush	↓	DRG neurons	SIRT1	SIRT1 ↑, miR-138 and SIRT1 are part of a mutual negative feedback loop, Neurite extension and outgrowth ↑, Axon regeneration in vivo ↑	(C.-M. Liu et al., 2013)
miR-206	Rat	CCI	↓	DRG neurons	BDNF/ MEK/ERK axis	BDNF ↑, MEK/ERK pathway activation ↑, Mechanical and thermal hypersensitivity ↑	(Sun et al., 2015)
miR-133b	Zebrafish	Spinal cord transection	↑	The nucleus of the medial longitudinal fascicle (NMLF)	RhoA	RhoA ↓, Regeneration of axons from NMLF ↑, Superior reticular formation ↑, Intermediate reticular formation ↑	(Ym et al., 2011)
miR-34c	Mouse	STZ- induced diabetes	↑	TG neurons	Atg4B	Atg4B, LC3-II ↓, Autophagy ↓, Wound healing ↓, Corneal nerve regeneration ↓	(J. Hu et al., 2019)
miR-9	Mouse	Sciatic nerve crush	↓	DRG neurons	FoxP1	FoxP1 ↑, Neurite extension and outgrowth ↑, Axon regeneration in vivo ↑	(J. Jiang et al., 2017)
miR-132	Mouse	N/A	Enriched in DRG neurons	DRG neurons	RASA1	RASA1 ↓, Neurite extension and outgrowth ↑	(Hancock et al., 2014)
miR-9 Let-7	Rat	Sciatic nerve crush	Let-7 ↓, miR-9 ↓	Sciatic nerve (Schwann cells), DRG neurons	Ntn1, DCC	Ntn1, Dcc production and secretion in Schwann cells ↑, Schwann cell migration ↑, Neurite extension and outgrowth ↑	(X. Wang et al., 2019)

migrate in hypoxic environments to carry out repair. A recent study found that hypoxia following sciatic nerve injury could induce upregulation of miR-132 within Schwann cells which functioned to promote Schwann cell migration, while a reciprocal inhibitory effect on migration was observed by downregulation of miR-132 (C. Yao et al., 2016, p. 3). miR-132 was reported to promote Schwann cell migration by directly targeting protein kinase AMP-activated non-catalytic subunit gamma 3 (PRKAG3), a regulatory subunit of the AMPK (C. Yao et al., 2016, p. 3). It is plausible, then, that enhanced SC migration might be associated with AMPK inhibition induced by miR-132, however, the predominance of PRKAG3 targeting by miR-132 in governing SC migration was not established and other miR-132 targets may also participate.

miR-221 and miR-222 have been reported to function as oncogenes by targeting cell cycle inhibitors and tumor suppressors (phosphatase and tensin homolog (PTEN), TIMP metallopeptidase inhibitor 3 (TIMP3)) to promote cell growth and tumor metastasis (Galardi et al., 2007; X. Liu et al., 2009). Peripheral nerve injury elevates expression from the miR-221/222 cluster in Schwann cells, and their upregulation is reported to promote Schwann cell proliferation and migration by inhibiting longevity assurance homologue 2 (LASS2). Elevation of miR-221 has also been observed in the spinal cord and isolated microglia in rat models of neuropathic pain (L. Xia et al., 2016, p. 1). miR-221 was found to directly target suppressor of cytokine signaling 1 (SOCS1), an important negative-feedback inhibitor of cytokine signaling which can reduce inflammatory responses. Intrathecal administration of miR-221 inhibitor promoted SOCS1 signaling and suppressed the activation of the NF-κB and p38 MAPK pathways, which in turn reduced neuroinflammation and attenuated mechanical and thermal hypersensitivity (L. Xia et al., 2016, p. 1). Further investigation is needed to determine whether the miR-221 upregulation locally in Schwann cells following injury also targets these inflammatory pathways in peripheral nerves to promote hypersensitivity.

The lncRNA NEAT1 has been demonstrated to undergo robust upregulation in the spinal cord in a CCI injury model (L.-X. Xia et al., 2018). NEAT1 silencing inhibited both mechanical and thermal allodynia following injury. NEAT1 was reported to elevate neuroinflammation and contribute to neuropathic pain development by promoting high mobility group box 1 (HMGB1) expression through the sponging miR-381 as a ceRNA (L.-X. Xia et al., 2018). NEAT1 is also upregulated in Schwann cells following sciatic nerve injury (X. Liu et al., 2019). In this context, a function for the upregulated NEAT1 in promoting Schwann cell proliferation and migration was supported using both gain and loss of function approaches. NEAT1 was reported to act by sponging miR-34a and relieving repression of the miR-34a-targeted transcript for special AT-rich sequence-binding protein-1 (Satb1) which is a positive regulatory of proliferation (X. Liu et al., 2019). This local regulatory role of NEAT1 in Schwann cells has yet to be linked to the development of pain, although it could potentially have participated in the reported effects of NEAT1 silencing (L.-X. Xia et al., 2018).

Multiple examples presented here support a pattern in which regulation of the same miRNA can modulate physiological changes in multiple cell types and can do so through targeting discrete transcripts. This

Table 4
Ncrnas in schwann cell responses following nerve injury.

ncRNAs/ Biogenesis regulators	Species	Model	Regulation	Location	Target	Physiological functions	Reference
miR-9	Rat	Sciatic nerve transection	↓	Schwann cells	CTHRC1/Rac1 GTPase axis	CTHRC1 ↑, Rac1 GTPase ↑, Schwann cell migration ↑	(S. Zhou et al., 2014, p. 9)
miR-1b	Rat	Electroacupuncture (EA) treatment	↓	Schwann cells	BDNF	BDNF ↑, Schwann cell migration and proliferation ↑, Schwann cell apoptosis ↓, Nerve conduction velocity ratio (NCV), sciatic functional index (SFI) in vivo ↑	(Y.-P. Liu et al., 2020)
Let-7 miRNAs	Rat	Sciatic nerve crush	↑ at Day 1, ↓ at Day 4 – Day 7, Rebounding at Day 14	Schwann cells	NGF	Temporal expression profile of Let-7 miRNAs was negatively correlated with NGF, Schwann cell migration and proliferation ↑, Axon regeneration in vivo ↑	(S. Li et al., 2015)
miR-132	Rat	Sciatic nerve transection	↑ by hypoxia	Schwann cells	PRKAG3	PRKAG3 ↓, Schwann cell migration ↑, Axon regeneration in vivo ↑	(Yao et al., 2016)
miR-221 miR-222	Rat	Sciatic nerve transection	↑	Schwann cells	LASS2	LASS2 ↓, Discharge of H + through V-ATPase ↑ Schwann cell migration and proliferation ↑	(B. Yu, Zhou, et al., 2012)
MALAT1	Mouse	Sciatic nerve crush	↑	Schwann cells	miR-129/BDNF axis	miR-129 ↓, BDNF ↑, Schwann cells migration and proliferation ↑	(G. Wu et al., 2020, p. 1)
NEAT1	Mouse	Sciatic nerve crush	↑	Schwann cells	miR-34a/Satb1 axis	miR-34a ↓, Satb1 ↑, Schwann cells migration and proliferation ↑, DRG neurite outgrowth ↑	(X. Liu et al., 2019)

might be expected when considering that transcriptomes may vary widely in both a qualitative and quantitative manner between cell types, giving rise to different predominant miRNA-targeting events in different settings. For example, upregulation of miR-132 following peripheral injury promotes both axon extension and Schwann cell migration, as well as being implicated in the development of neuropathic pain, although these effects are executed through different downstream signaling pathways (Hancock et al., 2014; Leinders et al., 2016; C. Yao et al., 2016). The let-7 family miRNAs provide another such example. At early stages following nerve injury, lowered let-7 levels in Schwann cells promote neurotrophic factor synthesis and secretion from Schwann cells, which enhances both axon outgrowth and Schwann cell proliferation (S. Li et al., 2015; X. Wang et al., 2019). Upregulation of let-7 at later stages following injury is also a prominent regulator to facilitate re-myelination of the peripheral nerves with discrete targets implicated (Gökbuget et al., 2015). Although effective nerve regeneration resolves neuropathic pain, miRNAs that facilitate nerve outgrowth and tissue repair may also concomitantly elicit elevated sensory responses in hyperalgesia. Further investigation to dissect the signaling networks and timing of ncRNA-mediated regulation of gene programs in peripheral tissue will be valuable to shed light on the intermingled relationship between nerve repair and persistent pain.

Discussion

Damage to the PNS can lead to the long-term sequela of chronic pain, particularly when the damage is either ongoing or unable to be appropriately resolved. Despite intensive study of how injured nerves contribute to persistent pain, there remain major gaps in our understanding, particularly with regards to underlying molecular mechanisms. While nociceptive pain is the normal response to noxious stimuli, enduring maladaptive forms of neuroplasticity create elevated nociceptive responses and hyperalgesia. Altered gene expression, including compartmentalized control at the post-transcriptional level is at the heart of persistently altered responses. Roles for ncRNAs in shaping local protein synthesis responses are now well-appreciated. In this review, we have discussed the dynamic regulation of ncRNAs, following injury, focusing on miRNAs and lncRNAs in discrete cell types of the PNS. Current understanding of the contribution of ncRNAs in neurons, Schwann cells, and immune cells to modulating persistent nociceptive plasticity underlying pain is summarized. With few exceptions, ncRNAs act to regulate the repression of target transcripts directly or indirectly. ncRNAs influence the translation of critical mediators of inflammation, growth factors, pain-associated molecules, and components of neurophysiological pathways contributing to neuronal excitation. Through these actions, ncRNAs impact neuroimmune interactions, neuronal survival and axon regeneration, intercellular communication, and the ectopic generation of action potentials in primary afferent processes. The ncRNAs and targets referenced in sections of this review are described in Fig. 1, Tables 1, 2, 3, and 4.

ncRNAs are also studied as potential biomarkers for disease diagnosis and prognosis, and ncRNA-based therapeutic approaches for treating nerve injury and pain management are under investigation (Yu et al., 2015; J. Zhang et al., 2018). Constraints to clinical use of miRNA-based therapies for gene modulation remain, including potential for deleterious side effects, short half-life, and complexities in delivery and penetration to target tissues (Aloe et al., 2012; S. Li et al., 2015; Manni et al., 2013). While manipulating ncRNAs in animal models, for example with miRNA agomirs and antagomirs, has revealed some promising outcomes, there is a need for the development of non-invasive approaches to deliver ncRNA modulators to the nervous system locally as an approach to diminish off-target effects (Yu et al., 2015). An insufficient understanding of the molecular mechanisms of ncRNA-mediated changes impacting pain development and persistence also presents a current obstacle to the therapeutic efficacy of ncRNA-based approaches. While the importance of ncRNAs in regulating responses to nerve injury

and the development of neuropathic pain is now supported by many investigations, there are fundamental aspects of this regulation which remain unclear. Traditionally, ncRNAs, in particular miRNAs, have been conceptualized as participating in the 'fine-tuning' of gene expression. Highly expressed miRNAs, however, can have more dramatic effects on regulating translation from targeted transcripts, and this may be especially observed when a miRNA or a family of miRNAs are highly expressed or work together. For instance, miR-132 is often highly expressed in cells of the nervous system, and members of the let-7 family of miRNAs have a shared seed sequence and typically have multiple highly expressed family members in mature cells. The extent to which individual miRNAs or miRNA families cooperate or work alone to achieve physiological effects on persistent pain following nerve injury remains poorly understood. Further, we lack sufficient understanding of how groups of miRNAs might be tuned collectively in peripheral tissues; the involvement of mechanisms governing miRNA stability, miRNA biogenesis, or co-sponging by ceRNAs are interesting possibilities. In addition, we lack an understanding of how alterations in ncRNAs following nerve injury are temporally regulated and what are potential mechanisms governing persistence.

As in many other fields of miRNA research, a quantitative genome-wide view of changes in miRNA:target interactions is lacking in models of persistent pain. Genome-wide approaches will be needed to characterize the network of miRNAs and their target mRNAs that are cooperatively dysregulated in the PNS following injury, and to gain a realistic understanding of the primary targets implicated in any given cell type or phase of response. Excitingly, molecular approaches to understanding RNA:RNA interactions have been pioneered and refined in recent years and might be successfully applied to questions of ncRNA function in persistent pain (H. Cao & Kapranov, 2022; Hafner et al., 2021). Several of these strategies allow the intermolecular ligation of miRNAs directly to target mRNAs within the RISC complex to form a single chimeric RNA molecule which can be subjected to high-throughput sequencing and mapping to provide genome-wide characterization of miRNAs and their target mRNAs (Bjerke & Yi, 2020; Hafner et al., 2021; Mills et al., 2022; Moore et al., 2015; Videm et al., 2021). An in-depth understanding of ncRNA:target RNA interactions in tissues of the peripheral nervous system, obtained through application of these broad and quantitative strategies, and others like them, is likely to provide insights needed to dissect the miRNA-target profiles which could contribute to the generation of pain. Additional technological developments in molecular tools and delivery strategies to permit precise and cell-type specific manipulation of ncRNA:target RNA interactions will also be key to revealing the next advances in this field (Mendes et al., 2022; Paunovska et al., 2022; Wei et al., 2020).

Author contributions

XL and MKM conceptualized the study. XL collected and organized information. XL, DSJ, and SE wrote the first draft of the manuscript. All authors contributed to reviewing, editing, and updating following versions of the manuscript. MKM supervised the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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