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Review

# MicroRNAs as modulators and biomarkers of inflammatory and neuropathic pain conditions

Hjalte H. Andersen [a,b], Meg Duroux [b], Parisa Gazerani [a,b,*]

[a] Center for Sensory-Motor Interaction, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark
[b] Laboratory of Cancer Biology, Biomedicine, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark

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ABSTRACT

The post-transcriptional regulator molecules, *microRNAs*, have emerged as important biomarkers and modulators of numerous pathophysiological processes including oncogenesis and cardiovascular diseases. Recently, a significant number of dysregulations in microRNAs have been reported in patients suffering from painful disorders such as complex regional pain syndrome, cystitis-induced chronic pain and irritable bowel disorder, in both affected tissues and the circulation. Moreover, microRNAs are known to be involved in pain processing based on several recent findings in animal models of inflammatory and neuropathic pain.

The basis of this review was to cover and summarize available articles in English encompassing "*microRNA* and *pain*". In animal pain models widespread microRNA modulation is present and manifests on multiple levels i.e.: the dorsal root ganglia, the spinal dorsal horn and the brain. Numerous functional *in vivo* studies have found that dysregulated microRNAs are involved in the post-transcriptional modulation of genes implicated in pain generation and maintenance. Lastly, a few animal studies have delivered promising results as to the possibility of applying microRNAs as therapeutics to alleviate established pain and several clinical studies have highlighted the potential in applying microRNAs as biomarkers in painful conditions such as complex regional pain syndrome and fibromyalgia. This review briefly introduces the basics of microRNAs, their biogenesis and function, and mainly focuses on the recent advances made in understanding the role of microRNAs in relation to pain processing and painful conditions. It also provides an overview of widely diverse methodological approaches and results with a potential for future implications of microRNAs in the diagnosis and treatment of pain.



**Contents**



* Corresponding author at: Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7D3, Aalborg Ø, DK-9220, Denmark.
*E-mail address:* gazerani@hst.aau.dk (P. Gazerani).
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## Introduction

Human disorders associated with significant pathological pain such as osteoarthritis (OA), post-herpetic neuralgia, diabetic polyneuropathy and migraine are all highly prevalent, reduce life quality for affected patients and thus represent a large socioeconomic burden (Berger et al., 2004; Manack et al., 2011; Pérez et al., 2012; Phillips, 2003). Moreover, these conditions share a high incidence of co-morbidities and largely suboptimal treatment possibilities (Finch, 2013; Pérez et al., 2012). Significant progress has been made in terms of identifying matrices involved in normal and pathological pain processing as well as understanding the molecular mechanisms underlying nociception and pain (Pace et al., 2006). Similarly, advances have been made in understanding the causes underlying pain chronification (Seifert and Maihöfner, 2011). Within the last six years, accumulating evidence has suggested that a class of small non-coding inhibitory RNAs known as microRNAs (miRNAs) play an important role in regulating pain-processing within a wide range of experimental models and clinical pain disorders (see Fig. 1) (Kynast et al., 2013a; Lutz et al., 2014; Niederberger et al., 2011). This review aims at presenting the advances made in understanding the role of miRNAs as micro-modulators, biomarkers and potential therapeutic entities of painful conditions.

### *Search methodology and structure*

Based on the PubMed entry: "(Pain OR nociception) AND (miRNA OR microRNA)", with no time limit on the 24th of April 2014, 120 indexed articles were identified, demonstrating that research on microRNAs in relation to pain is still very limited. All publications were curated based on title and abstract; from those, 49 were found relevant and included, whereas 69 were excluded. It is important to note that this particular search strategy is not intended to cover all miRNA alterations in diseases that can give rise to pain per se. For example, various cancers, such as glioblastoma, involve extensive miRNA dysregulation and can result in excruciating pain (Edvardsson and Persson, 2012), however, this example and similar areas are not dealt with in this review since the primary focus of the literature in such fields are inherently related to the miRNA-involvement in oncogenesis and not pain processing (Edvardsson and Persson, 2012; Møller et al., 2013). The studies included herein can be broadly subdivided into the following 3 categories of which several overlap: 1) explorative studies of miRNA-alterations induced by modeled pain conditions *in vivo*, i.e. both pain related to inflammation and neuropathy, 2) studies investigating miRNA alterations in patients suffering from various conditions related to pain, and 3) studies that explore the functional properties of one or more specific miRNA in relation to a particular pain

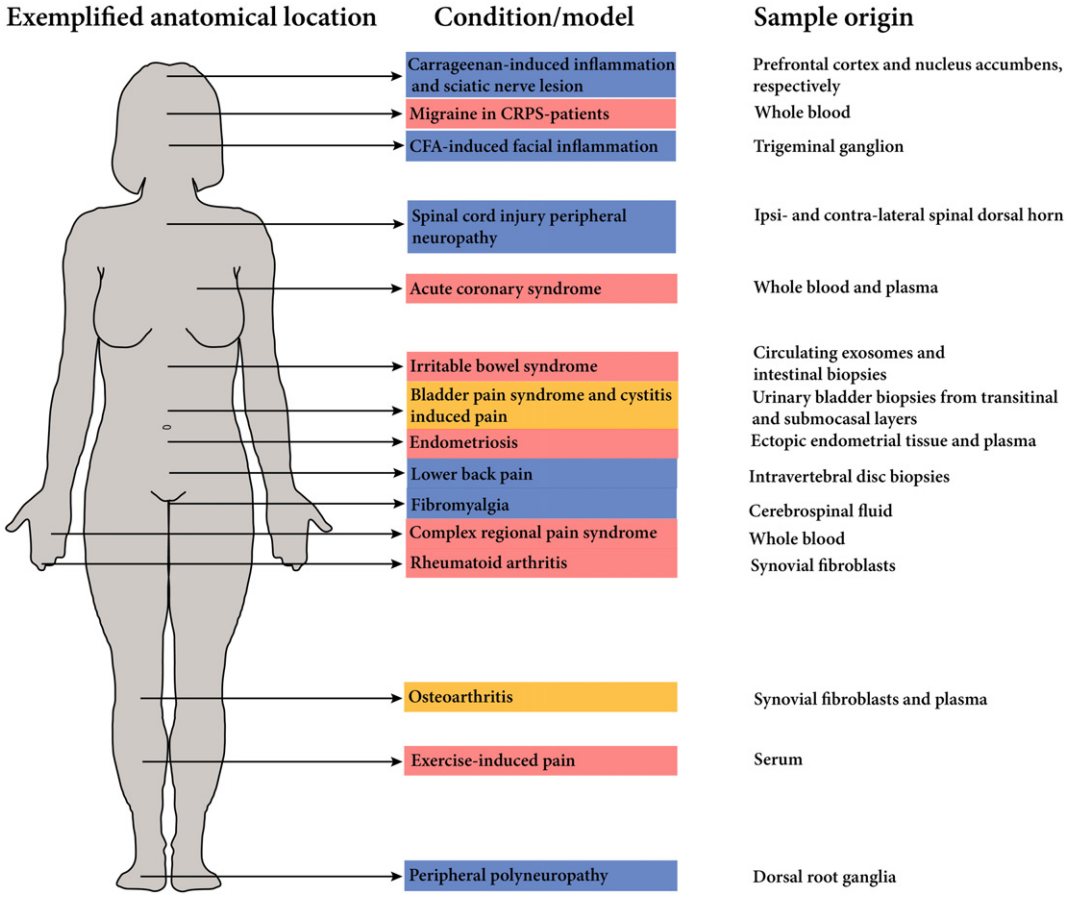



**Fig. 1.** Clinical pain condition and *in vivo* pain models accompanied by significant miRNA modulation and the tissue(s) where the miRNA changes manifest. Typical pathological locations are represented. Blue = animal surrogate model of pain, red = clinical pain conditions, orange = animal surrogate model of pain and clinical pain conditions.

model (*in vitro* and *in vivo*). The review is sectioned in accordance with the commonly perceived etiology of pain models as either inflammatory or neuropathic pain (Pace et al., 2006). Studies of miRNA dysregulation in patients with conditions associated with significant recurrent or chronic pain are classified according to various somatic origins.

### *MicroRNA structure and function*

miRNA is a novel class of non-coding single-stranded RNA of 19–24 nucleotides with the ability to modulate a large proportion of the genome post-transcriptionally (Bartel, 2009; Lagos-Quintana et al., 2001). They bind to the 3′ untranslated region (UTR), or occasionally 5′ UTRs, of the multiple mRNA targets to which they exhibit imperfect, or sometimes, perfect complementarity. This enables one specific miRNA to inhibit the translation of multiple genes (Thomson et al., 2011; Ørom et al., 2008). The first miRNA was discovered in *Caenorhabditis elegans* in 1993 and named: lin-4 (Lee et al., 1993). Later, upon discovery of let-7, which was found conserved in several species, miRNA-regulation was recognized as an omnipresent entity in eukaryotes (Pasquinelli et al., 2000; Reinhart et al., 2000).

The biogenesis of miRNA starts with the transcription of miRNA-genes by RNA polymerase II, giving rise to *pri-miRNA*, which is then poly-adenylated, upon which it is cleaved by Drosha to become *pre-miRNA* and transported out of the nucleus by Exportin-5 (Yi et al., 2003). Dicer then cleaves the pre-miRNA of which normally only one strand, the *guide-strand*, is merged into the RNA-induced silencing complex (RISC). RNA-silencing post-transcriptionally is facilitated by the binding of miRNA attached to RISC, to the respective mRNA 3′ UTR, resulting in translational inhibition (Winter et al., 2009). Some miRNAs are selectively excreted via lipoproteins or micro-vesicles, functioning as a mode of intercellular communication, a notion that is of crucial importance in relation to the potential of miRNA as biomarkers (Chen et al., 2012; Stoorvogel, 2012). For more information on miRNA biogenesis, please refer to the available comprehensive reviews (Tran and Hutvagner, 2013; Winter et al., 2009).

Today, miRNAs are established, as crucial micro-modulators of normal cellular homeostasis and accordingly, the dysregulation of miRNAs has been associated with a wide range of pathological conditions such as cancer (Calin and Croce, 2006; McManus, 2003), cardiovascular diseases (Vickers et al., 2014), and neurodegenerative disorders (Abe and Bonini, 2013). The expression of miRNAs in pathological specimens or biofluids normalized to corresponding non-pathologic samples is under extensive scientific investigation (Jia et al., 2014). Selected miRNAs are subsequently subjected to *in silico* and/or *in vitro* validation to elucidate their specific target genes. Accordingly, studies on miRNAs in relation to pain are rapidly emerging with a main focus on individual miRNAs, their role in various conditions and whether silencing/mimicking them could be a potential treatment strategy. In addition, the application of miRNAs as diagnostic tools in an array of diseases, including painful conditions, identification of patients at risk for development of e.g. chronic pain conditions and the follow-up of the treatment course with conventional drugs are under extensive investigation (Chen et al., 2014; Im et al., 2012; Willemen et al., 2012).

## Molecular mechanisms of pain: a role for microRNAs?

Multiple polymorphisms, affecting genes involved in neuronal signal transduction, have been associated with altered pain response phenotypes (James, 2013). These polymorphisms most predominantly, affect genes involved in: 1) action potential generation e.g. the $Na^+$-channel SCN9A, 2) signal transmission e.g. the serotonin related SLC6A4, and 3) endogenous pain modulation e.g. the μ-opioid receptor 1 (MOR1) (James, 2013; Reyes-Gibby et al., 2007). However, the overall prevalence of these and similar genotypes remains low when compared to the high prevalence of chronic pain conditions without a hereditary etiology. This highlights the great importance in pathological pain mechanisms not related to the genomic layout (Breivik et al., 2006; Houlden et al., 2006).

### *Central and peripheral sensitization*

Alteration in protein expression is one of the main characteristics in development of a long-term hyper-excitability of peripheral nociceptive and central neurons, which can contribute to development or maintenance of chronic pain (Gold and Gebhart, 2010). As such, the process is inherently subject to potential regulation by miRNAs, centrally as well as peripherally.

In the periphery, inflammatory mediators such as prostaglandin $E_2$ ($PGE_2$), interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα) release from the immune cells, keratinocytes, growth factors such as granulocyte–macrophage colony-stimulating factor, nerve growth factor (NGF) and neuropeptides such as calcitonin gene-related peptide (CGRP), substance P and histamine from local nociceptors, are involved in development or maintenance of hyperalgesia (Gangadharan and Kuner, 2013). This inflammatory soup prompts activity in multiple gene pathways including MAPK3 and JAK-STAT-signaling and recruits multiple downstream enzymes such as phospholipase C and phosphoinositide 3-kinase. This causes phosphorylation and de novo transcription of nociceptive molecules such as transient receptor potential cation channel subfamily V member 1 (TRPV1) and $Na_v1.8$, ultimately leading to hyper-excitability of the nociceptive Aδ- and C-fibers (Gold and Gebhart, 2010; Julius and Basbaum, 2001).

Central sensitization is caused by synaptic plasticity, activation of glial cells, decreased signal transmission thresholds and decreased endogenous modulation (Sandkühler, 2009; Scholz and Woolf, 2007; Woolf, 2011). Excitatory synaptic communication between first order neurons and spinal cord neurons is largely facilitated by the neurotransmitter glutamate and modulated by factors such as CGRP and brain-derived neurotrophic factor (BDNF). Accordingly, post-synaptic glutamatergic receptors play an important role in modulating synaptic transmission following persistent nociceptive activity (Ji et al., 2003). Changes in spinal function include long-term potentiation of synapses as well as an increase in neuronal and glial hyper activity or hyper responsiveness in the spinal dorsal horn (SDH), leading to overall increased pain sensitivity (Ji et al., 2003; Sandkühler, 2009). In this relation, it is now established that significant miRNA alterations occur in the SDH and the DRG under both inflammatory and neuropathic pain conditions.

### *MicroRNA facilitated regulation of pain genes*

Importantly, genetic, epigenetic and transcriptional alterations manifest on a protein-level and considering that >60% of the mammalian genes are miRNA-targets, it is inherent that miRNAs are involved in the post-transcriptional regulation of proteins crucial in pain processing pathways (Friedman and Farh, 2009). In accordance, the dysregulation of miRNAs targeting key regulators of pain processing such as γ-aminobutyric acid-α1 ($GABA_{α1}$) (Sengupta et al., 2013), cyclooxygenase 2 (Akhtar and Haqqi, 2012; Park et al., 2013), TRPV1 (Li et al., 2011) and multiple $Na^+$ and $Ca^{2+}$-channels (Favereaux et al., 2011; Li et al., 2011; von Schack et al., 2011) has been observed in various surrogate models of pain. Similarly, it has been shown that miR-23b regulates the expression of MOR1 (Ni et al., 2013) and that opioid-tolerance associated with prolonged morphine-administration is potentially a consequence of miR-23b upregulation, thus extending the role of miRNA to involve modulation of endogenous analgesic mechanisms (Wu et al., 2008). This highlights the importance of understanding the mechanisms behind the transition from acute physiological pain to pathological chronification, and in the context of this review particularly mapping to which extend miRNA-induced transcriptional repression of genes is involved in pain pathophysiology.

## MicroRNAs in pain and nociception

### *MicroRNAs involved in acute and prolonged inflammatory pain*

A number of different *in vivo* models of inflammation have been used to investigate the role of miRNA in inflammatory pain processing. Generally, widespread miRNA alterations are observed upon pain induction (see Table 1). In a study by Zhao et al. (2010) it was shown that Dicer knockout mice had an attenuated pain response to inflammation assessed by carrageenan injection into the hind paw, highlighting that miRNA modulation may predominantly constitute a detrimental mechanism in the context of inflammation induced pain and hyperalgesia (Zhao et al., 2010). This section highlights findings pertaining to the role of miRNA modulation upon induced inflammation.

To date, four studies using Freund's complete adjuvant-induced (CFA) inflammatory hyperalgesia have been published. In a pioneering study in 2007, it was shown that inflammation induced by injection of CFA into the masseter muscle of rats caused significant downregulation of 7 different miRNAs (see Table 1) in the mandibular branch of the trigeminal nerve, amongst them was miR-124 widely described as a key miRNA in pain-processing (Bai et al., 2007). Also using CFA, Kusuda et al. (2011) applied a different approach only investigating four preselected brain-specific miRNAs of which miR-1 and miR-16 expression was markedly downregulated for 7 days, but surprisingly upregulated in the SDH along with miR-206, 24 h after induction. The same year, miR-143 was shown to be downregulated in the DRG upon CFA-induction but notably not in a neuropathic pain model applying sciatic nerve transection (Kusuda et al., 2011). The authors suggested Vcan1/2, known to modulate neurogenesis, as a putative target based on a corresponding ipsilateral increase in mRNA, but a luciferase-based target validation was not performed (Kusuda et al., 2011). Most recently, it was confirmed that miR-134, previously demonstrated to be decreased under neuropathic conditions (Bai et al., 2007), was downregulated in the DRG upon inflammatory induction with CFA and that it was inversely correlated with MOR1-expression. The study subsequently applied a luciferase-assay to validate MOR1 as a target of miR-134 elucidating a potential endogenous pain modulation mechanism and highlighting a novel therapeutic opportunity (Ni et al., 2013).

### *MicroRNAs in animal models of osteoarthritis*

Several studies have used animal models of OA to study the miRNA changes in association with the pathogenesis of this prevalent and painful condition. Firstly, a prominent increase in miR-155 in synovial fibroblasts and monocytes was revealed in patients with rheumatoid arthritis (RA) (Stanczyk et al., 2008). It was later discovered that miR-146a was significantly increased in peripheral blood mononuclear cells in RA (Pauley et al., 2008). Elaborating on these results, Li et al. (2011) used the MIA OA-model analyzing miRNA-expression both in the DRG and the SDH and analyzed miR-146a modulation in human synoviocytes (Li et al., 2011). Surprisingly, in rodent models of OA a steep decrease in miR-146a expression in both the DRG and SDH was seen (as opposed to the known upregulation in peripherally affected cells). Expanding on that finding, the influence of miR-146a was investigated applying transient transfection of miR-146a in astrocytes and microglia, resulting in a significant decrease in pro-inflammatory transcripts such as: TNFα, COX2, nitric oxide synthase (iNOS) and interleukin 6 (Li et al., 2011). In a study comparing cultured chondrocytes from healthy and OA donors miR-558 was found to have significantly decreased in the latter. The study further showed that miR-558 deficiency is inducible by IL-1β and confirmed COX2 as a direct target mRNA, highlighting its potential importance in joint inflammation (Park et al., 2013). The same group also used a surgical animal model of OA analyzing miRNA-expression both in the DRG and the SDH, here, a significant reduction in the expression of miR-146a and miR-183 was found (X. Li et al., 2013). This finding concurred with increased mRNA levels of a number of pro-inflammatory mediators such as NFκB, TNFα and IL-1β, but luciferase validation was not conducted on these potential targets. Interestingly, the study conducted a series of loss/gain of function studies on microglia (BV2 cell line) and astrocytes supporting the notion of miR-146a as being a key regulator of inflammation, as previously reported by the same group (Li et al., 2011).

### *MicroRNAs as potential therapeutic targets for inflammation*

miR-124 has been found centrally downregulated in two studies applying different models of peripheral inflammatory hyperalgesia; intraplantar IL-1β-injection and formalin application and is validated to target MeCP2, previously implicated in nociception (Kynast et al., 2013b; Willemen et al., 2012). Interestingly, miR-124 appears to modulate the reactivity of microglia promoting M1 to M2 switch; thus potentially decreasing central sensitization (Willemen et al., 2012). When applied intravenously miR-124 and anti-miR-124 caused decreased and increased pain behavior, respectively, albeit only significantly in a subset of the assessment timeframe (Kynast et al., 2013b). Other known centrally acting miRNA alterations include upregulation of miR-155 and miR-233 in the prefrontal cortices of rats upon carrageenan-facilitated facial inflammation (Poh et al., 2011). Within visceral inflammation, a very recent study investigated modulation of miRNA in the developing spinal cord following neonatal cystitis in a rodent-model applying zymosan. A steep increase of miR-181a was revealed concomitantly with an apparent repression of the $GABA_{A\alpha1}$-subunit. Subsequent administration of the $GABA_A$-receptor agonist, muscimol, did not attenuate the viscero-motor response (VMR)

**Table 1**
Overview of results from studies on miRNA modulation in animal surrogate models of inflammatory pain. Superscript numerals annotate a miRNA and its target gene(s). Only luciferase-validated mRNA targets are included. The abbreviation behind individual highlighted miRNAs denotes the origin of the sample: HC = hippocampus, SC = spinal cord, SDH = spinal dorsal horn, DRG = dorsal root ganglion, and ACC = anterior cingulate cortex.

| Study | Pain model | Highlighted miRNAs (sample origin) | Central/peripheral | Aberrant miRNAs | Luciferase-validated targets |
|---|---|---|---|---|---|
| Bai et al. (2007) | CFA-induced trigeminal pain | miR-10a, miR-29a, miR-98, miR-99a, miR-124, miR-134, miR-183↓ (TG) | Both | 7 | |
| Li et al. (2011) | Inflammatory joint pain | miR-146a↓ (DRG, SDH)/miR-146a↑ (JC) | Both | 1 | |
| Tam Tam et al. (2011) | CFA-induced pain | miR-143↓ (DRG) | Peripheral | 1 | |
| Kusuda et al. (2011) | CFA-induced pain | miR-1↑, miR-16↑, miR-206↑ (DRG) miR-1↓, miR-16↓, miR-206↓ (SDH) | Both | 3 | |
| Poh et al. (2011) | Facial inflammation | miR-155↑, miR-233↑ (PC) | Central | 1 | |
| Willemen et al. (2012) | IL-1β-induced inflammatory hyperalgesia | miR-124↓ (SCM) | Central | 1 | |
| Xu et al. (2012) | IL-1β-induced inflammation in chondrocytes | miR-194↑ (JC) | Peripheral | 1 | SOX5 |
| X. Li et al. (2013) | Surgically induced joint pain | miR-146a, miR-183↓ (DRG) | Peripheral | 9 | |
| Kynast et al. (2013b) | Formalin-induced inflammatory pain | miR-124a↓ (SDH) | Central | 1 | MECP2 |
| Ni et al. (2013) | CFA-induced pain | miR-134↓ (DRG) | Peripheral | 1 | MOR1 |
| Park et al. (2013) | Inflammatory joint pain | miR-558↓ (JC) | Peripheral | 1 | COX2 |
| Pan et al. (2014) | CFA-induced pain | miR-219↓ (SC) | Central | 1 | CAMK2G |

to colon distension in rats with neonatal cystitis, whereas in cystitis-induced adult rats the drug produced significant decrease in VMR (Sengupta et al., 2013). The authors concluded that it is likely that miR-181a is directly involved in toning spinal cord inhibition, unmasking excitatory pathways to facilitate prolonged or even chronic pain and hyperalgesia (Sengupta et al., 2013). Very recently, Park et al. (2014) reported that extracellular miR-let-7b induces inward currents in rat DRG through coupling between Toll-like receptor-7 and the nociceptive ion-channel transient receptor potential cation channel subfamily A. Furthermore, the study elucidated a direct nociceptive effect of miR-let-7b *in vivo*, documented that miR-let-7b is released from nociception neurons upon activation, and showed a reduction in formalin-induced pain by concomitant administration of miR-let-7b-inhibitor (Park et al., 2014). This report indicates that circulatory miRNAs could be as physiologically relevant as intracellular miRNAs and highlights their biomarker potential.

### *MicroRNAs involved in neuropathic pain*

Lesions to the somatosensory nervous system frequently give rise to neuropathic pain, generally classified as either central or peripheral. It is estimated that ≈8% of the Western population suffers from one or more subcategories of painful neuropathy with diabetic small-fiber neuropathy being the most common subetiology (Torrance et al., 2006). Several studies investigating changes in miRNA expression upon induced neuropathy in rodent models have demonstrated a significant dysregulation in numerous miRNAs (see Table 2). A study by Genda et al. (2013) found that 111 miRNAs were significantly modulated in the SDH after chronic constriction injury (CCI) in mice, but no further functional characterization was performed (Genda et al., 2013). Illustrating the lack of consolidation in this research field, a recent study, also using CCI was unable to show any significant difference between CCI- and sham-operated mice (Brandenburger et al., 2012). An early study utilizing a sciatic nerve injury model in mice investigated both the differential expression of miRNA in dorsal root ganglion (DRG) neurons compared to scam injured mice, and also the effect of nerve injury on the proteins involved in miRNA biosynthesis. While subunits of the RISC were highly upregulated, levels of various p-body machinery proteins differed significantly between groups, indicating that not only miRNA-deregulation but also regulatory proteins involved in the miRNA-processing pathway could be of importance in the peripheral response to injury (Wu et al., 2011). In a L5 spinal nerve ligation model, 63 miRNAs were found dysregulated, 59 of which were concomitantly dysregulated in the ipsilateral L4 DRG suggesting that miRNA changes in adjacent uninjured afferents may also contribute to the development and continuation of neuropathic pain. The study did not elaborate further on these projected miRNA alterations and their underlying cause (von Schack et al., 2011). Another recent study using a spinal nerve ligation model utilized genome-wide miRNA sequencing in two genetically similar rat strains displaying opposite responses to neuropathic injuries, i.e. pain-prone and pain-resistant. The study discovered a 3-miRNAs signature being highly downregulated in the pain-prone rat strain and used *in silico* target prediction to associate the miRNAs rno-miR-30d-5p and rno-miR-125b-5p with the neuropathic pain related genes, TNF and BDNF (Bali et al., 2014).

Several studies have investigated neuropathy-induced miRNA alterations at the central level. Imai et al. (2011) found that sciatic nerve lesion in mice induced significant downregulation of miR-200b and -429 in post-synaptic neurons of nucleus accumbens and that this downregulation corresponded with increased levels of DNA (cytosine-5)-methyltransferase 3A (DNMT3a). The authors proposed that the DNMT3a increase associated with decreased levels of miR-200b and -429 is involved in the generation of dysfunction of the mesolimbic motivation/valuation circuitry linking prolonged nociceptive stimuli with co-morbid conditions such as anxiety and sleep disturbances (Imai et al., 2011). In a similar study using CCI in mice, the hippocampal formation was analyzed using TaqMan low-density arrays and 51 miRNAs were found to be significantly altered compared to contralateral sham surgery. With complementary qRT-PCR the study investigated the downregulation of miRNAs miR-125b and -132 at days 7 and 15 post injury but conducted no miRNA target-validation (Arai et al., 2013). In a recent study using bilateral CCI in rats and performing miRNA microarray analysis on DRG, SDH, hippocampus and anterior cingulate cortex, a significant upregulation of miR-341 was observed in DRG-neurons and a downregulation of miR-181a-3p, -203 and -541-3p was observed in the SDH, demonstrating miRNA alterations in both the CNS and PNS in response to chronic sciatic constriction. None of these miRNAs was further functionally analyzed. In contrast to the study by Arai et al. (2013), no significant miRNA modulations were observed in the hippocampus, representing a substantial discrepancy in the literature (H. Li et al., 2013).

**Table 2**
Overview of results from studies on miRNA modulation in animal surrogate models of neuropathic pain. Only luciferase-validated mRNA targets are included. The abbreviation behind individual highlighted miRNAs denotes the origin of the sample: TG = trigeminal ganglion, SDH = spinal dorsal horn, DRG = dorsal root ganglion, SCM = spinal cord microglia, JC = joint chondrocytes, and PC = prefrontal cortex.

| Study | Pain model | Highlighted miRNAs/(sample origin) | Aberrant miRNAs | Central/ peripheral | Luciferase-validated targets |
|---|---|---|---|---|---|
| Aldrich et al. (2009) | Spinal nerve ligation | miR-96↑, miR-182↑, miR-183↑ (all DRG) | 3 | Both | |
| Liu et al. (2009) | Contusive spinal cord injury | miR-137, miR-181a, miR-219-2-3p, miR-7a↓, miR-21↑ (all SDH) | 269 | Central | |
| Nakanishi et al. (2010) | Spinal cord injury | miR-223↑, miR-124a↓ (SC) | 2 | Central | |
| Imai et al. (2011) | Sciatic nerve lesion | miR-34c↓, miR-200b↓, miR-429↓ (all ACC) | 17 | Central | |
| Favereaux et al. (2011) | Spinal nerve ligation | miR-103↓ (DRG) | 1 | Peripheral | CACNA1C, CACNA2D1, CACNB1 |
| Kusuda et al. (2011) | Spinal nerve ligation and axotomy | Axotomy: miR-1 (↑SDH/↓DRG), miR-16↑ (SDH), miR-206↑ (SDH)<br>Spinal nerve ligation: miR-1↓ (DRG), miR-206↓ (DRG) | 3 | Both | |
| Wu et al. (2011) | Sciatic nerve crush | miR-124↓, miR-221↑, miR-142-5p↑, miR-21↑ (All DRG) | 4 | Peripheral | |
| Im et al. (2012) | Spinal cord injury | miR-23b↓ (SDH) | Unspecified | Central | NOX4 |
| Genda et al. (2013) | CCI | miR-21, miR-221, miR-500 (all DRG) | 111 | Peripheral | |
| Arai et al. (2013) | CCI | miR-125b↓, miR-132↓ (both HC) | 51 | Central | |
| H. Li et al. (2013) | CCI | miR-341↑ (DRG), miR-203↓ (SDH), miR-541-5p↓ (SDH), miR-181a-1-3p↓ (SDH) | 1 | Central | |
| Chen et al. (2014) | CCI | miR-96↓ (DRG) | 1 | Peripheral | |
| (Li et al., 2014) | Bilateral constriction injury | miR-203↓ (SDH) | Unspecified | Central | RAP1A |

*MicroRNAs as potential therapeutic targets for neuropathic pain*

In the light of four recent studies, the outlook of applying anti-miRNAs/miRNA-mimics to treat neuropathic pain and hyperalgesia seems bright. In streptozotocin-induced diabetic neuropathy in rats, a miRNA-construct targeting $Na_v\alpha$-subunits was delivered by a herpes simplex virus-based vector successfully reversing cold allodynia and thermal and mechanical hyperalgesia (Chattopadhyay et al., 2012). In another comprehensive study, intrathecal administration of miR-23b-mimics significantly alleviated mechanical and thermal hyperalgesia in a mice model of spinal cord injury. Furthermore, miR-23b was shown to target NADPH oxidase 4 (NOX4), an inflammation-promoting enzyme, also known to decrease production of the inhibitory neurotransmitter GABA through inhibition of glutamic acid decarboxylase (Im et al., 2012). Similarly, miR-124 (which is highly expressed in quiescent microglia) was shown to shift the M1/M2 balance towards the anti-inflammatory M2 phenotype and to decrease mechanical hyperalgesia and pain behavior in a spared nerve model in mice (Willemen et al., 2012). Most recently, Chen et al. (2014) showed that CCI causes a steep decrease of miR-96 in DRG neurons, coinciding with an increase in $Na_v1.3$, an ion-channel implicated in neuropathic hyper-excitability and a predicted target of miR-96. Subsequently, the study proved intrathecal injections to be efficient in alleviating both mechanical and thermal hyperalgesia associated with the CCI procedure (Chen et al., 2014). It is evident that miRNAs have a potential as specific biomarkers and possibly therapeutic entities within neuropathic conditions and new studies on functional miRNA characterization and exploration of delivery methodology could hold promise in future targeted therapy of neuropathic pain.

## MicroRNAs in clinical pain conditions

As described, it is evident that animal models of neuropathic and inflammatory pain demonstrate widespread miRNA alterations and furthermore that many of these alterations are detrimental to the given condition (Chen et al., 2014; Genda et al., 2013). This section highlights novel findings on the implication of miRNAs from clinical painful conditions with diverse characteristics and origin. In the context of investigating the link between miRNAs and pain processing, it is important to note that particularly when it comes to clinical pain conditions it is unclear to which extent miRNAs merely aggravate the underlying pathogenesis subsequently leading to pain perception and not pain processing itself.

The most comprehensive body of literature is available on the subject of knee arthritis, first and foremost OA and RA. Human specimens from patients clearly indicate that miRNAs are entwined in the pathogenesis of RA and OA, potentially contributing to cartilage degeneration and possibly even pain chronification (Furer et al., 2010; Stanczyk et al., 2008; Yu et al., 2011). It is beyond the scope of this review to summarize the findings of miRNAs implication within OA, RA and autoimmune diseases in general (refer to Furer et al., 2010 for more on this particular topic).

*MicroRNAs in visceral pain conditions*

In several visceral painful conditions such as irritable bowl syndrome (IBS), bladder pain syndrome (BPS), endometriosis and cystitis-induced chronic pain (CICP) miRNA dysregulation has been reported. In IBS, the miRNA profile appears to facilitate an increased permeability of the gastrointestinal tract (Zhou et al., 2010). A noteworthy study by Verne and colleagues (2010) demonstrated that miR-29a is markedly increased in patients with IBS in intestinal biopsies and in a subset of diarrhea-predominant IBS patients' miR-29a was found significantly upregulated in circulating miRNA-containing exosomes (see Table 3). The study used a luciferase-reporter to validate that miR-29a targets the glutamine synthetase gene GLUL, thus decreasing enterocytic glutamine levels and aggravating the increased intestinal permeability (Zhou and Verne, 2011; Zhou et al., 2010). In a study of BPS, 31 miRNAs were differentially expressed and a direct correlation between the increased expression of miR-449b and miR-500 concomitantly with downregulation of the substance P receptor NK1-receptor was found (Sanchez Freire et al., 2010). The authors suggested this to constitute a miRNA-dependent adaptive mechanism to the prolonged NK1R overexpression which was previously described in BPS (Marchand et al., 1998; Sanchez Freire et al., 2010). In endometriosis, characterized by menstrual cycle-dependent pelvic pain, a great deal of recent research has revealed the influence of miRNAs. The first study reporting widespread miRNA dysregulation in endometriosis was published in 2007 (Pan et al., 2007) and 45 studies have been published since then on that subject.[1] Notably, Hawkins et al. (2011) performed a full microRNAome analysis of endometriosis patients and found 22 miRNAs to be dysregulated. The study further investigated the highly upregulated miR-29c and elucidated its ability to significantly inhibit several important genes involved in extracellular matrix function such as collagen type VII A1 (COL7A1). Lastly, the same study also validly pointed out the extensive discrepancy present in terms of the specific miRNAs found across similar studies but ascribed it to methodological differences e.g. sampling time in relation to menstrual cycle (Hawkins et al., 2011). In the highly prevalent pain disorder, lower back pain, Zhao et al. (2014) investigated one of the frequent underlying causes being intervertebral disc degeneration (IDD). Here, miRNA expression in the nucleus pulposus was compared between IDD patients and acute intervertebral injury patients giving rise to a large miRNA signature, but no further analysis was performed (Zhao et al., 2014).

*MicroRNAs as biomarkers in pain disorders*

Investigating miRNAs as diagnostic and prognostic biofluid-derived biomarkers is well progressed in various fields, particularly oncology and cardiology, but is novel in relation to pain conditions (Ahmad et al., 2013; Kinet et al., 2013). Research in miRNAs are of great interest in terms of biomarker potential since they are present in virtually all biofluids, exhibit more superior stability than mRNA and appear to be highly sensitive to slight changes in various physiological processes (Jung et al., 2010; Kemppainen et al., n.d.; Tomaselli et al., 2012).

In an innovative study by Orlova et al. (2011), whole blood samples were taken from 41 patients with complex regional pain syndrome (CRPS) and 20 controls upon which analysis of miRNA expression, cytokines and numerous clinical parameters were conducted (see Table 3). Unsurprisingly, cytokines such as CCL2 and VEGF were notably elevated in the CRPS group compared to control and a CRPS miRNA-signature was evident. Interestingly, extensive correlation analyses revealed that 4 miRNAs (miR-296-5p, -532-3p, -361-3p and -30d) were positively correlated with CRPS-associated pain level, miR-150 was correlated with the occurrence of migraine within the CRPS patient cohort and an extensive array of miRNAs was found to correlate with the levels of circulating cytokines (Orlova et al., 2011). A recent study with a similar design investigated the miRNA profile of the cerebrospinal fluid in fibromyalgia patients and identified 10 miRNAs differentially expressed between affected patients and healthy controls. Most notably, the study found that decreased levels of miR-145-5p in the CSF were associated with reported symptomatology i.e. pain intensity and fatigue (Bjersing et al., 2013).

The prospect of applying miRNAs as biofluid-derived biomarkers in pain conditions is enticing due to their high specificity, e.g. circulating miRNA-signatures have been ascertained to discriminate between eccentric and concentric exercise (Banzet et al., 2013). However, numerous obstacles are present when using circulating miRNAs: 1) it remains unclear why and to which extent miRNAs are selectively

[1] NB. Studies that include "*endometriosis*" and "*microRNA*".

**Table 3**
Examples of painful disorders where serum microRNA aberrations are associated with symptomatology. *Notice that these are proposed endogenous control miRNAs, but are found significantly dysregulated. ↑/↓ = increase/decrease.

| Reference | Condition | MicroRNA(s) | Sample / sample size |
|---|---|---|---|
| Orlova et al. (2011) | Complex regional pain syndrome | (↓) miR-939, -25, -7c, -7a, -7b, -320b, -126, -629, -664, -320, -1285, -625, -532-3p, -181a<br>(↑) RNU48*, RNU44*, miR-720, -1201 | Whole blood/41 patients, 20 controls |
| Bjersing et al. (2013) | Fibromyalgia | (↓) miR-21-5p, 145-5p, 29a-3p, 99b-5p, 125b-5p, 23a-3p, 23b-3p, 195-5p, miR-223-3p | Cerebrospinal fluid/10 patients, 20 controls |
| Zhou et al. (2010) | Irritable bowel syndrome | (↑) miR-29a | Serum micro-vesicles/19 patients, 10 controls |
| Wang et al. (2013) | Endometriosis | (↑) miR-199a miR-122<br>(↓) miR-145a-3p, -141-5p, -542-3p, -9-3p | Serum/10 patients, 10 controls (screening) \| 60 patients,<br>25 controls (validation) |
| Beyer et al. (2014) | Osteoarthritis | (↓) let-7e, miR-454, -885-5p | |

exported (Boon and Vickers, 2013), 2) there are numerous quality issues associated with sampling, particularly hemolysis and low isolation yields, and 3) plasma miRNA expression is highly affected by various hormonal and metabolic factors (Tomaselli et al., 2012).

## Conclusion and future directions

Despite being a subfield in its infancy, it is clear that miRNA alterations are essential in a variety of pain models and in clinical conditions characterized by severe pain (Kynast et al., 2013a). Until now studies have been conducted either in animal pain models or in fewer cases within a patient cohort posing inherent limitations as to the translatability between these two types of studies. The use of human surrogate models have been beneficial in improving understanding of pain processing by temporarily recreating concise pain symptoms such as spontaneous burning pain, heat hyperalgesia or cold allodynia (Andersen et al., 2014; Arendt-Nielsen and Yarnitsky, 2009). Studies mapping the local and systemic miRNA alterations likely associated with induced local inflammation in widely used models such as the heat/capsaicin, ultraviolet B and NGF models (Arendt-Nielsen and Yarnitsky, 2009) are warranted.

Within animal models of neuropathic and inflammatory pain such as rodent spinal nerve ligation and CFA-induced inflammation, widespread miRNA modulation is observed (Bai et al., 2007; Genda et al., 2013). It appears that miRNA alterations occur more rapidly in response to inflammatory pain, and some suggest it to be an adaptive mechanism aimed at pain reduction, as opposed to miRNA alterations in response to neuropathic pain suggested mainly to be a detrimental process (Bali and Kuner, 2014; Gheinani et al., 2013). Despite the fact that numerous miRNAs are frequently reported aberrantly expressed, only modest overlap between dysregulated miRNA such as miR-103 in neuropathy and miR-146a in inflammation is present in the literature (Favereaux et al., 2011; Li et al., 2011; Pauley et al., 2008; Yamasaki et al., 2009). Further research is warranted to adequately elucidate whether this is a consequence of limited published data or high specificity between miRNA alterations between various pain conditions. Interestingly, a few miRNAs, such as miR-183, have been found consistently downregulated in both neuropathic and inflammatory pain conditions while others, such as miR-1, have opposite responses between neuropathic and inflammatory models and even within different neuropathic pain models (Bali and Kuner, 2014; Kusuda et al., 2011).

Although administration of anti-miRs and miR-mimics has already been successfully applied in animal models of neuropathic and inflammatory pain, it is necessary to obtain consistent knowledge about the role of miRNAs in pain processing during various normal and pathological pain conditions before any diagnostic or therapeutic utilization can be accomplished (Chattopadhyay et al., 2012; Chen et al., 2014; Im et al., 2012; Willemen et al., 2012). Frequently, a large number of miRNAs are found dysregulated in a given condition (Genda et al., 2013). This is, at the same time, an obstacle and also an opportunity. The obvious challenge lies in increased complexity and choosing the most promising miRNA(s) for further investigation. To overcome this challenge several strategies can be utilized: 1) the median absolute deviation can be applied to assess the most differentially expressed miRNAs across samples in combination with statistical testing, 2) *in silico* target prediction algorithms can be used to predict feasible targets relevant for pain processing, and 3) specific promising miRNAs can be tested individually in miRNA transfection studies. As for the opportunity related to the fact that many miRNAs are often found dysregulated in a given condition, increased specificity is the primary gain. As such, miRNAs as biomarkers are promising not only in terms of diagnosis, but also in relation to patient stratification. A seemingly high level of specificity could hold promise in stratification of heterogeneous patient populations, currently difficult to subcategorize. The literature is growing dramatically in terms of reporting aberrantly expressed miRNAs in multiple pain conditions; however, functionally well-characterized miRNAs is highly lacking and needs particular attention (Arai et al., 2013; Genda et al., 2013).

Another pronounced bottleneck is represented by the problem of distributing miRNA-mimic or anti-miRNA to the target tissue, particularly when it comes to delivering miRNAs across the blood brain barrier, which would be relevant to formulate a centrally acting analgesic. Novel results indicate a great potential of exosomes, already known to carry microRNAs in cell-to-cell communication and to deliver siRNA to target cells (Chen et al., 2012; Johnsen et al., 2014). This approach was utilized by Alvarez-Erviti et al. (2011), who applied exosomes expressing neuron-specific targeting surface peptides by systemic injection. This enabled cell specific delivery of the siRNA-cargo across the blood brain barrier (Alvarez-Erviti et al., 2011). Although promising, some concerns have been made as to whether exosomal cell-to-cell interaction is physiologically relevant and whether exosome-carried therapeutics will prove clinically feasible (Sverdlov, 2012).

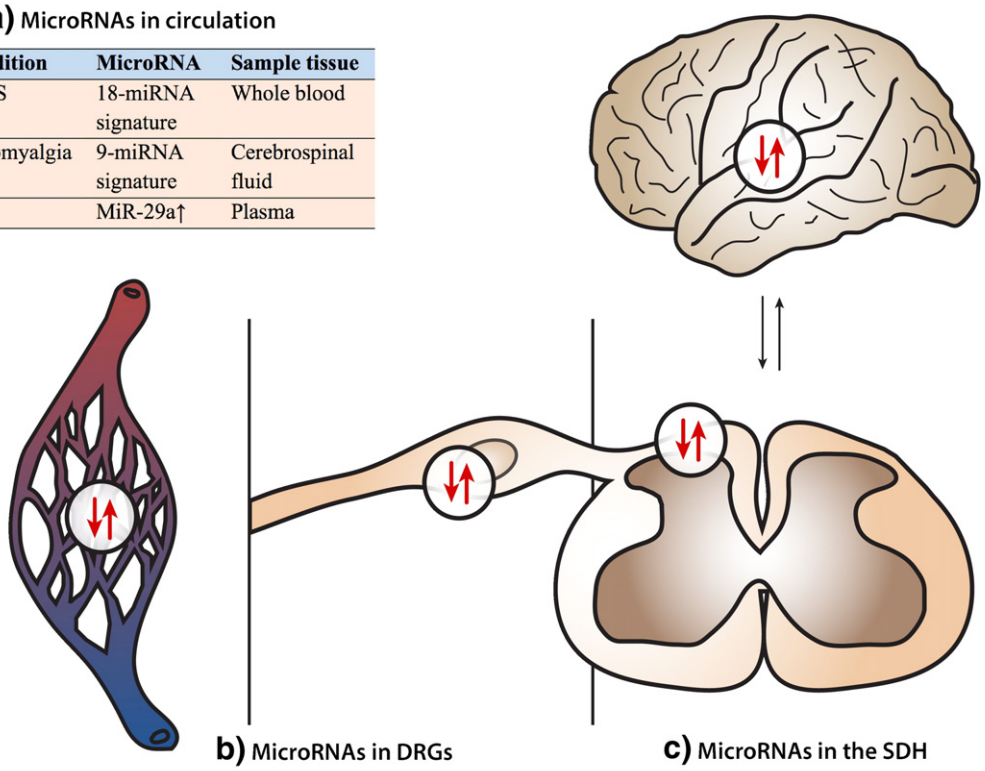
Intricately, pain gives rise to miRNA alterations on multiple levels (see Fig. 2). In circulation, miRNAs-signatures have been discovered in e.g. IBS and CRPS-patients (Orlova et al., 2011; Zhou et al., 2010). In local tissues miRNA dysregulation in response to pain involve residing primary afferents, fibroblasts and keratinocytes e.g. in post-operational skin inflammation (Sun et al., 2012). Knowledge is scarce regarding the purpose of circulating miRNAs and local cell-to-cell interactions mediated by miRNAs, but these fields are of great interest in regards to biomarkers and potential formulation of topical analgesics, respectively. In the DRG and the SDH widespread miRNA dysregulation has been documented in response to both neuropathic and inflammatory pain and it is evident that miRNA expression is selectively modulated between the SDH and DRG neurons in response to the exact same injury. For instance, miR-16 expression was significantly reduced in the DRG, but upregulated in the SDH after CFA-induced inflammation in mice, i.e. exhibiting opposite expressional response between peripheral and central compartments (Kusuda et al., 2011). Many of these studied miRNA-driven alterations prompt the initiation or maintenance of a more excitable phenotype, thus increasing the conductance of nociceptive stimuli (Chen et al., 2014; Zhao et al., 2010). It is known that both microglia and astrocytes

**d)** MicroRNAs in the brain

| Condition | MicroRNA | Gene target |
|---|---|---|
| Inflammatory pain | MiR-200b, MiR-429↓ | DNMT3a |
| Neuropathic pain | MiR-155↓ | C/EBP* |

**a)** MicroRNAs in circulation

| Condition | MicroRNA | Sample tissue |
|---|---|---|
| CRPS | 18-miRNA signature | Whole blood |
| Fibromyalgia | 9-miRNA signature | Cerebrospinal fluid |
| IBS | MiR-29a↑ | Plasma |



**b)** MicroRNAs in DRGs

| Condition | MicroRNA | Gene target |
|---|---|---|
| Inflammatory pain | MiR-134↑ | MOR1 |
| Neuropathic pain | MiR-183↓ | CACNA1D* |

**c)** MicroRNAs in the SDH

| Condition | MicroRNA | Gene target |
|---|---|---|
| Inflammatory pain | MiR-181a↑ | GABRA1 |
| | MiR-124↓ | MECP2 |
| Neuropathic pain | MiR-29a↓ | CACNA1C |
| | MiR-23b↓ | NOX4 |

**Fig. 2.** Locations of miRNA alterations in response to induced pain and painful disorders. The tables at each level list examples of well-investigated miRNAs and their corresponding mRNA targets. MiRNA modulation is reflected in: the circulation, DRG neurons, SDH, glial cells and in several brain areas. DRG = dorsal root ganglion and SDH = spinal dorsal horn. *Not validated with a luciferase-reporter assay.Red arrows denote miRNA up- and downregulation and the specified locations.

are involved in central sensitization and that miRNA dysregulation in these cells is correspondingly associated with CNS hypertrophy and increased reactivity (Bhalala et al., 2012; Ponomarev et al., 2011). Circulatory miRNAs are also present in the cerebrospinal fluid and here specific miRNAs have been linked to pain in fibromyalgia patients (Bjersing et al., 2013). Lastly, miRNA alterations have been mapped in several brain matrices associated with higher pain processing in rodent models of pain (Poh et al., 2011).

In summary, miRNAs are rapidly emerging as pivotal players involved in pain from the first single study in the field in 2007 (Bai et al., 2007) to 37 publications in 2013 alone. These small non-coding RNA molecules represent promising potential biomarkers and therapeutic targets in a variety of human diseases, including pain conditions. However, pronounced bench-to-bedside hindrances warrants further studies before miRNAs can be applied clinically in pain patients for prognosis, diagnosis, follow-up of the treatment course, and potentially novel treatment strategies.

## Conflict of interest

No conflict of interest to declare.

## Author contributions

All authors contributed in the conception, writing and discussion of this manuscript.

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