

MicroRNA: A Major Key in Pain Neurobiology



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Abstract

MiRNAs are single-stranded small noncoding RNAs that consist of approximately 22 nucleotides, that are involve in a wide range of biological processes including pain physiopathology. Because of their role as master switches in regulation and signaling pathways through modifications in nociceptive receptors, ion channels, pro-inflammatory molecules, emotional and cognitional behaviors associated with pain, the triggered enthusiasm for miRNAs as promising therapeutic targets is still active. Furthermore, the expression of specific miRNA can be helpful to predict treatment response in patients which suffer pain conditions that are poorly controlled by the currently available analgesics. This evidence is supported in several researches with animal pain models that we briefly review in this article to approximate in the understand of the role and neurobiology process through miRNA represents a major key for future therapeutics in pain, emphasizing in the neuropathic pain condition.

Keywords: MicroRNA; Neurobiology; Neuropathic pain

Introduction

Neuropathic pain (NP) represents one of main causes of chronic pain, perhaps trailing only osteoarthritis as a cause [1]. One of the keys to understand the biology of neuropathic pain is to know that's is caused by an injury in a nervous tissue and that nociceptive pathways are involve in the lesion [2]. In the clinical practice, the most frequent NP origins are the neurons of dorsal root ganglia (DRG) and trigeminal ganglia (TG) in mechanical, metabolic and toxic lesions as traumatic injury, herpes zoster, diabetes, or cancer chemotherapy, all this kind of pathologies promotes functional changes in the initiation and maintenance of NP [3,4].

The several changes observed in neuropathic pain condition are well represented in two major symptoms, allodynia and hyperalgesia. Both symptoms are observed in patients and as signs in animal models of chronic pain such as the spinal nerve ligation (SNL), consisting in a tight ligation of L5 and L6 spinal nerves were Fukuoka et al. [5] described a down-regulation of the inhibitory γ -amino butyric acid receptor A (GABAA) in the dorsal root ganglia (DRG). In spared nerve injury (SNI) were shown an up-regulation of interleukin-1 β (IL-1 β) in the prefrontal cortex of rats [6]. And many other changes can be observe in every pre-clinical model of pain which includes up-regulation of interleukin-6 (IL-6) [7], neurokinin-1 receptor in the dorsal horn [8], down regulation of dopaminergic D1 and D2 receptors in the anterior cingulate cortex in a rat model [9] just to mention a few. Clearly, this changes in the substances and receptors regulation are product of an altered gene expression in the nociceptive

pathways. One of the most recent studied mechanisms that explains the pathogenesis and play a crucial role in fine-tuning gene expression [10] in the chronic pain is MicroRNAs (miRNAs) regulation, that are involve in a wide range of biological processes [11]. In this review we will focus in the role and neurobiology process through miRNA represents a major key for future therapeutics in pain, emphasizing in the NP condition.

Biology and mechanisms of miRNA

MiRNAs are single-stranded small noncoding RNAs that consist of approximately 22 nucleotides. The genomic location of miRNAs can be broadly divided into intergenic (between genes) or intronic (embedded into a gene) [11]. After the transcription of a coding DNA protein is expressed the precursor messenger RNA (pre-mRNA) which conformation includes 4 regions, 5'-untranslated region (UTR), the protein-coding exon, the noncoding intron, and the 3'-UTR, that determines the main targets of miRNA [12]. The intronic or intron-derived microRNA (Id-miRNA) is formed in the in-frame introns and the intergenic miRNAs are set between independent transcription units [13], both has the capability of degrading messenger-RNA (mRNA) and inhibit protein translation so they share not only functional but also structural properties. With the only difference that intronic miRNA are typically transcribed from the same promoter as their host genes (Pol II) and require RNA splicing machinery [14-16] while intergenic RNAs genes have their own transcription regulatory elements [13].

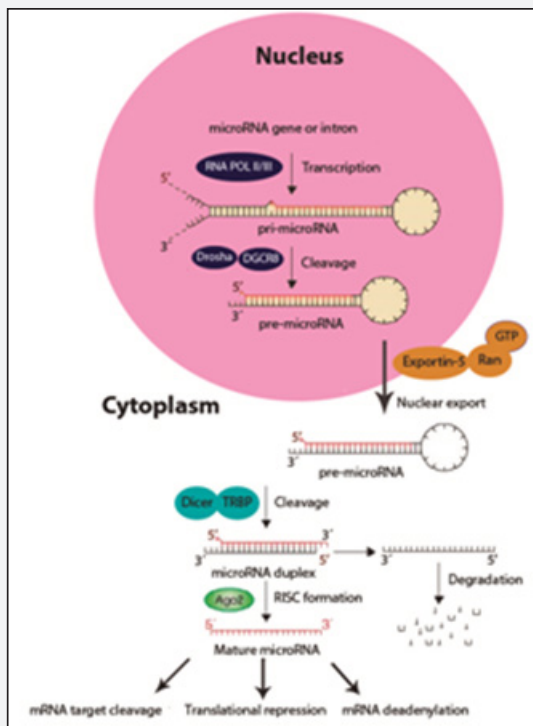


Figure 1: The linear processing pathway of miRNA. The formation of the RNA-induced gene silencing complex (RISC) is capable of executing RNA interference (RNAi)-related gene silencing, concluding in mRNA deadenylation, translational repression and mRNA cleavage.

In Figure 1 is represented the genesis and mechanism by which the interaction between miRNA, the target mRNA and the RNA-induced gene silencing complex (RISC) suppress the gene expression. This process begin with the excision of the primary precursor microRNA (pri-miRNA) by the RNA polymerase type-II (Pol-II) [17], this pri-miRNA at certain concentration can make a negative feedback to Pol-II. Then if the pri-miRNA is origin in

an exon, it will be cropped into the hairpin-shaped pre-miRNAs by nuclear RNase III Drosha [18] or by spliceosomal components if comes from introns to form a mature precursor miRNA (pre-miRNA). This pre-miRNA is exported out of the nucleus to the cytoplasm by a member of a Ran-dependent nuclear transport receptor family, the exportin-5 (Exp5) [19] where is cleaved to the Dicer-like nucleases to form mature miRNA [20]. Finally the miRNA is coupled to a ribo nuclear particle (RNP) to get the RISC which is capable of executing RNA interference (RNAi)-related gene silencing, concluding in the inhibition of the protein translation [21].

MiRNA and Pain

The comprehension of the extensive pathways involved in the genesis of pain put in evidence that the genetic basis play a major role in pain biology [22]. In the very last years the focus of researches have been in looking not in an specific target or individual receptor but instead in a “major switch” that would regulate multiple gene products and orchestrate multiple pathways [23] and the recent evidence propose miRNA to be that switch. The miRNAs have been implied in inflammation [24] process and other pain conditions such as neuropathic pain [25] and fibromyalgia [26]. This both common clinical problems are usually poorly controlled by the currently available analgesics [27], the reason might be the complex and multiple processing of nociceptive information in pathological conditions [28]. The changes in this processing are the cause of phenomes like hyperexcitability that can be induced by a posttranslational modulation of ion channels, such as voltage-gated sodium channels [29] or long term potentiation (LTP) and disinhibition that are product of synaptic modifications [30]. So, this phenomes initiated by altered processing in nociceptive pathways respond to certain structures like spinal glial cells, especially microglia and astrocytes that also plays a major role in pain modulation [31] and can be govern by epigenetic mechanisms such as DNA methylation, histone modification, and miRNA expressions [32].

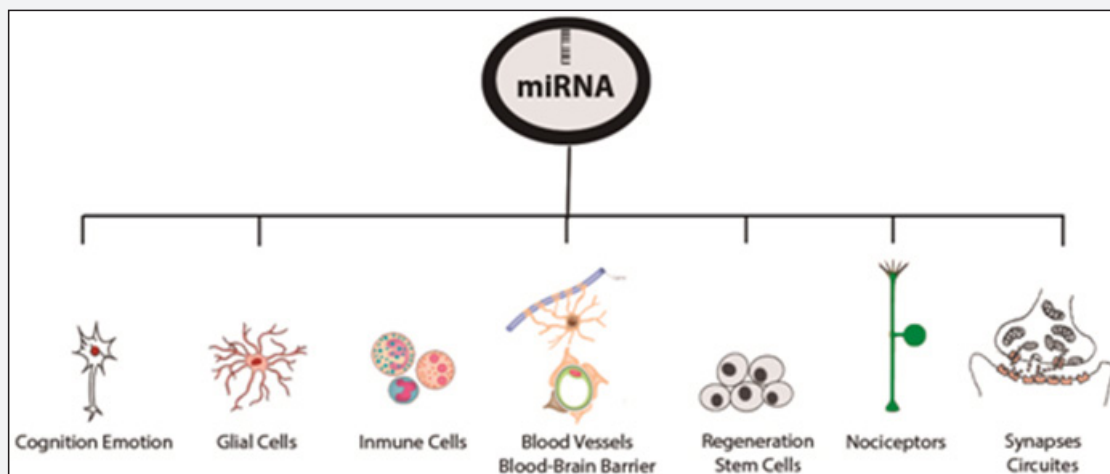


Figure 2 : miRNA plays a “major switch” role in many pathways involved in pain development and maintenance including behavioral, emotional and cognitional changes.

This supports the evidence of the critical role of miRNAs in pain biology, but not only at molecular, network or synaptic level, the miRNAs are implied in behavioral, emotional and cognitional changes [33] that affects pain perception [34] (Figure 2). However, the expression of miRNAs in DRG, spinal cord, and brain regions such as the limbic system and prefrontal cortex can vary from the different causes of pain [4]. The Table **Table 1**: Characterized Non coding RNAs in various painful conditions.

1, resumes some of the most representative miRNAs expressed in certain pathologies and animal model of acute and chronic pain, excluding neuropathic pain that will be considered in the next section. Figure 2. miRNA plays a “major switch” role in many pathways involved in pain development and maintenance including behavioral, emotional and cognitional changes.

Model	ncRNAs	Expression	Tissue	Reference
Formalin injection	miR-124a	Down	Murine ipsilateral dorsal horn neurons	Kynast et al. [35]
	miR-29a, -98, -99a, -124a, -134, -183.	Down	Rat ipsilateral trigeminal ganglion	Suzuki et al. [38] Bai et al. [39]
CFA	miR-1, -16, 206	Down	Rat ipsilateral DRG neurons	Kusuda et al. [40]
	miR-1, -16, 206	Up	Rat ipsilateral spinal dorsal horn neurons	
	miR-143	Down	Murine ipsilateral DRG neurons	Tam et al. [41]
	miR-219	Down	Spinal cord	Pan et al. [42]
Osteoarthritis	miR-199a, -127-5p	Down	Human chondrocytes	Akhtar et al. [43] Park et al. [44]
	miR-146a	Up	Human Synoviocytes	Li et al. [45]
Bone cancer	miR-1a-3p	Up	DRG	Bali et al. [46]

In the case of acute pain, the intra plantar formalin injection, was shown to decrease miR-124a expression in murine nociceptive spinal neurons in the ipsilateral horn [35], which importance seems to be related to the Methyl CpG binding protein 2 (MeCP2) a multifunctional epigenetic regulator that is best known for its role in the neurological disorders [36] and inflammatory pain [37]. Also, the tongue heat hyperalgesia following complete Freund’s adjuvant (CFA) injection shown that MeCP2 is involved in regulation of the transient receptor potential vanilloid 1 (TRPV1) expression in TG neurons [38], supporting the evidence of the down regulation of miRNA-124a for the expression of MeCP2. Other works revealed by a real-time reverse-transcription polymerase chain reaction (RT-PCR) a significant, but differential, downregulation of mature miR-10a, -29a, -98, -99a, -124a, -134, and -183 in the ipsilateral mandibular division (V3) of the TG within 4hr after CFA [39], this down regulation of miRNA releases the translation inhibition of target mRNAs, thus yielding more proteins that may be relevant to the development and/or maintenance of inflammatory pain as Bai et al. [25] conclude. In 2011 Kusuda et al. [40] found that CFA-induced inflammation significantly reduced miRs-1-16 and -206 expression in DRG. Conversely, in the spinal dorsal horn all three miRNAs monitored were up regulated [40]. Tam et al. [41] demonstrate for the first time that miR-143 expression in DRG nociceptive neurons is declined in response to inflammation [41]. More recently, Pan et al. [42] using a CFA model concluded that methylation-mediated epigenetic modification of spinal miR-219 expression regulates chronic inflammatory pain by targeting calcium/calmodulin-dependent protein kinase II

γ (CaMKII γ) which regulates NMDAR signaling and central sensitization [42].

In human chondrocytes with IL-1 β in vitro stimulation, revealed that the treatment with p38- mitogen-activated protein kinase (MAPK) inhibitor (SB202190), enhanced the expression of miR-199a* which can directly target COX-2 mRNA and reduce protein expression levels [43]. Considering the IL-1 β as a major mediator in chronic pain, described that miR-127-5p regulates MMP-13 expression and IL-1 β -induced catabolic responses in human chondrocytes too [44]. Finally, another miRNA, the miR-146a expressed at reduced levels in DRGs and dorsal horn of the spinal cords from rats with Osteoarthritis (OA)-induced pain significantly modulates inflammatory cytokines and pain-related molecules (e.g. TNF α , COX-2, iNOS, IL-6, IL8, RANTS and ion channel, TRPV1) [45]. In cancer-associated pain, another form of chronic pain, miR-1a-3p plays an important role attenuating the mechanical hypersensitivity [46], however in this pain condition, it might been implied a large list of miRs.

Role and Expression of miRNAs in Neuropathic pain

The role of miRNA in the regulation of nociception, endogenous analgesia and in the circuitries and cognitive, emotional and behavioral components involved in pain is expected to shed new light on the enigmatic pathophysiology of neuropathic pain [24]. Therefore disruption of miRNA processing in primary afferent pathways is sufficient to inhibit injury-induced long-term development of chronic pain-related behaviors, this affirmation is supported in a large evidence of investigations we resumed in Table 2.

Table 2: Characterized Noncoding RNAs in neuropathic pain condition.

Model	ncRNAs	Expression	Tissue	Reference
SCI	miR-21	Up	Spinal cord	Bhalala et al. [50]
				Strickland et al. [51]
	miR-124a	Down	Spinal cord	Nakanishi et al. [53]
				Strickland et al. [52]
				Strickland et al. [51]
	miR-223	Up	Spinal cord	Nakanishi et al. [53]
	miR-23b	Down	Spinal cord	Im et al. [54]
	miR-212	Down	Spinal cord	Wang et al. [55]
	miR-449a	Up	Spinal cord	Zhu et al. [56]
SNL	miR-7a, -21	Down/Up	DRG	
				Sakai et al. [58]
				Suzuki [59]
	miR-96, -182, -183	Down	DRG	Aldrich et al. [60]
	miR-103	Down	Spinal Cord	Favereaux et al. [61]
	miR-183	Down	DRG	Lin et al. [62]
	miR-195	Up	Spinal cord	Shi et al. [63]
	miR-30b	Up	DRG	Shao et al. [64]
			Su et al. [65]	
CCI	miR-7a, -21	Down/Up	DRG	Sakai et al. [4], Sakai et al. [38]
	miR-539	Down	Anterior cingulate cortex	Ding et al. [67]
	miR-93	Down	Spinal cord	Yan et al. [68]
	miR-183	Down	Spinal dorsal horn	Xie et al. [69]
	miR-145	Down	Spinal cord	Pang et al. [70]
Bilateral CCI	miR-203	Down	Spinal cord	Li et al. [71]
Axotomy	miR-21, -222	Up	DRG	Zhou, et al. [72]
Nerve crush	miR-21, -142-5p, -221	Up	Sciatic nerve	Wu et al. [73]
	miR-124a	Down	Sciatic nerve	

NcRNA (Noncoding RNA), SCI (Spinal cord injury), SNL (Spinal nerve ligation), CCI (Chronic constriction injury).

To start explaining the role of miRNA in neuropathic pain, let's first mention some of the main animal models that have been developed in this area. First the spinal cord injury (SCI) was proposed by Allen AR in 1911 [47] then in [48], adapted the Allen's method by a brief laminectomy performed at the T9–10 thoracic vertebrae level to expose the spinal cord at T10 and inducing the SCI by New York University Impactor device [49], with this method it has been possible to correlate the injury of the spinal cord with the regulation and expression of miRNAs like miR-21, miR-124a, miR-23b, miR-223, miR-449a and miR-212 [50-56]. Spinal nerve ligation (SNL), the left L6 transverse process is removed to expose the L4 and L5 spinal nerves then the L5 spinal nerve is carefully isolated, tightly ligated with 3-0 silk thread, and transected just distal to the ligature [57], with this method it's been studied the miRNAs miR-7a, -21, -96, -182, -183, -103, -195 [58-63] and more recently with miARN-30b [64,65]. The chronic constriction injury (CCI) model was proposed by Bennett and Xie in 1988 [66], in this model the right

sciatic nerve is tied loosely with four ligatures by chromic cat gut 4-0, the lastly works with this method revealed the expression of miR-7a, -21, -539, -93, -183, -145 and -203 [58,59,67-71]. The axotomy model consist in a transection of the sciatic nerve at a point approximately 1 cm distal to the exit point of spinal nerve roots, after Axotomy the expression of miR-21 and miR-222 increased in DRG [72]. Finally, the Nerve crush model is achieved after expose sciatic nerve and crush in the mid-thigh for 15sec with a fine hemostat, in the day 4 and 7 post injury the three most highly up regulated miRNAs was miR-21, miR-142-5p, and miR-221 [73]. Now we'll mention some of the most representative and lastly found miRNAs involved in neuropathic pain development.

The miR-21 is expressed in all the neuropathic pain models, [54] demonstrated that miR-21 transcripts are physiologically regulated by peripheral nerve injury. Their role appeared to be enhance neurite outgrowth from DRG neurons by targeting

the Sprouty2 protein (SPRY2) 3' UTR region in rats after axotomy. More recently, [69] studied the role of miR-183 in the development of neuropathic pain using the CCI model they revealed that miR-183 can suppress AMPA receptors by inhibiting the mammalian target of rapamycin (mTOR)/vascular endothelial growth factor (VEGF) pathway, which alleviates the mechanical hypersensitivity associated with inflammation and neuropathy [74]. Shao et al. [64] evidenced that one of the major targets in neuropathic pain, the voltage-gated sodium channel Nav1.7 are directly target by miR-30b. The expression of Nav1.7 increases in nociceptive neurons during the development of inflammatory hyperalgesia, while the knockdown or ablation of Nav1.7 expression relieves inflammatory pain and hyperalgesia [75]. Finally, [70] study suggested that miR-145 serves an important role in the development of neuropathic pain through regulating RREB1 expression and the PI3K/AKT signaling pathway which serves an important role in vascular endothelial growth factor (VEGF)-induced hyperalgesia [76].

Future Approaches and Conclusion

The studies reviewed in this article may us consider the microRNA's as potential targets and biomarkers for prediction and treatment of several pain conditions. Because of their role as master switches in regulation and signaling pathways through modifications in nociceptive receptors, ion channels, pro-inflammatory molecules, emotional and cognitional behaviors associated with pain, the triggered enthusiasm for miRNAs as promising therapeutic targets is still active. However, challenges with respect to the use of miRNA-based therapeutics in humans remain to be further explored [77]. When we can fully understand the role of miRNAs in pain mechanisms, it will be possible to maximize miRNAs potency while minimizing off target toxicity and immunogenicity to provide great benefit for clinical diagnostic and therapeutic applications.

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