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MicroRNA and chronic pain: From mechanisms to therapeutic potential

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ABSTRACT

Chronic pain is a major public health issue with an incidence of 20–25% worldwide that can take different forms like neuropathic, cancer-related or inflammatory pain. Chronic pain often limits patients in their daily activities leading to despair. Thus, the goal of treatments is to relieve pain sufficiently to enable patients to go back to a normal life. Unfortunately, few patients with chronic pain obtain complete relief from the analgesics that are currently available. It is thus of prime importance to get a better understanding of chronic pain mechanisms to design new therapeutic strategies and pain-killers. In this sense, the study of microRNA (miRNAs) in chronic pain conditions could lead to a breakthrough in pain management. miRNAs have emerged as master regulators of gene expression in the nervous system where they contribute to neuronal network plasticity. The involvement of miRNAs in the maladaptive plasticity mechanisms of chronic pain is now well documented. Here, we review studies conducted in different animal models and in patients that screened chronic pain-related miRNAs and their targets. Clinical studies suggest that miRNAs expression could reflect the high variability among pain patients that could help to categorize patients and finally lead to personalized therapies. We also point out the different strategies investigated to design miRNA-based analgesics. Finally, we highlight the current miRNA-based clinical trials to hypothesize their potential as therapeutic tool for chronic pain.

Contents

Abbreviations: BDNF, brain-derived neurotrophic factor; BPS, bladder pain syndrome; CamKII, Ca^{2+}/calmodulin-dependent protein kinase II; Cav1.2-LTC, Cav1.2-comprising L-type calcium channel; CCI, chronic constriction injury; CFA, complete Freund's adjuvant; CRPS, complex regional pain syndrome; CSF, cerebrospinal fluid; Cx43, connexin 43; DRG, dorsal root ganglia; $GABA_A$, γ-aminobutyric acid receptor A; GRK2, G protein–coupled receptor kinase; HCV, hepatitis C virus; HMGB1, high-mobility group box-1; IBS, irritable bowel syndrome; IL-6, interleukin 6; IL-1β, interleukin 1β; LNA, locked nucleic acids; LPS, lipopolysaccharide; MeCP2, methyl CpG binding protein 2; MOR, μ opioid receptor; MRE, miRNA Recognition Element; mRNA, messenger RNA; miRNA, microRNA; MVC, motor vehicle collision; NK1R, neurokinin 1 receptor; NOS2A, nitric oxide synthase 2; piRNAs, Piwi-interacting RNAs; pri-miRNA, primary-miRNA; RISC, RNA-induced silencing complex; siRNA, small interfering RNA; SNI, spared nerve injury; SNL, spinal nerve ligation; SOCS1, suppressor of cytokine signaling 1; TRPA1, transient receptor potential ankyrin 1; TLR7, toll-like receptor 7; TNF-α, tumor necrosis factor alpha; UGT1A, UDP-glucuronyl transferase; UTR, untranslated region.

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1. Introduction

Chronic pain is a major clinic issue with an incidence of 20–25% worldwide; in Europe it affects 19% of the adult population, seriously reducing the quality of their social and working lives (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). In the United States of America, more than 100 million people are affected by chronic pain with an annual cost of more than $600 billion (Gereau et al., 2014). Chronic pain disorders are difficult to treat due to their diversity (Kress et al., 2013). Spontaneous pain results from the stimulation of a primary nociceptive afferent that makes synapse in the dorsal horn of the spinal cord, and from here, pain information travels to supra-spinal areas (prefrontal cortex, cingulate, and parietal cortex) *via* thalamus for further processing. The establishment of chronic pain can arise from long-term sensitization at any level of this pathway (Ligon, Moloney, & Greenwood-Van Meerveld, 2016). The most common features of chronic pain are allodynia and hyperalgesia. Allodynia is a central pain sensitization state where a stimulus that does not usually provoke pain is inducing a pain response. Hyperalgesia results also from pain sensitization and can be defined as an increased sensitivity to painful stimuli resulting in an exaggerated pain sensation. One of the mechanisms involving peripheral and/or central sensitization is the altered regulation of gene expression. Initial studies of gene expression regulation date back to late 80s (for review see Hökfelt, Zhang, & Wiesenfeld-Hallin, 1994). More recently, regulation of gene expression has been shown to occur in nearly all models of pain, and affect a broad array of targets all along pain pathways. For instance, in the chronic pain model of spinal nerve ligation (SNL), consisting in a tight ligation of L5 and L6 spinal nerves, leading to mechanical allodynia and heat hyperalgesia, it was first described that inhibitory γ-aminobutyric acid receptor A ($GABA_A$) is down-regulated in neurons of the Dorsal Root Ganglia (DRG) (Fukuoka et al., 1998). In the spinal cord of animals with peripheral nerve injury it has been shown that the up-regulation of interleukin-6 (IL-6) mRNA (Arruda, Colburn, Rickman, Rutkowski, & DeLeo, 1998) and neurokinin-1 receptor in the dorsal horn was correlated with thermal hypersensitivity (Taylor & McCarson, 2004). Besides, in the supra-spinal areas, it has been shown that downregulation of dopaminergic D1 and D2 receptors occurs in the anterior cingulate cortex in a rat model of neuropathic pain (Ortega-Legaspi et al., 2011) and the upregulation of interleukin-1β (IL-1β) in the prefrontal cortex of rats with spared nerve injury (SNI) (Apkarian et al., 2006). Thus, it is clear that altered gene expression in the pain pathways is one of the mechanisms of chronic pain. The next step is to understand how genes are dys-regulated in chronic pain conditions and to eventually find a way to normalize gene expression and thus relief pain.

Gene expression can be modulated by different regulators acting at both the transcriptional and the translational level. In this review, we will consider the regulation exerted by a class of regulators receiving more and more interest in the field of pain, the microRNAs (miRNAs).

MicroRNAs are small non-coding RNAs that regulate gene expression by translational inhibition or mRNA degradation (Bartel, 2009). They are highly conserved in closely related animals and many are also conserved among animal lineages (Ambros, 2003; Aravin et al., 2003; Lagos-Quintana, Rauhut, Meyer, Borkhardt, & Tuschl, 2003; Lim, Glasner, Yekta, Burge, & Bartel, 2003), which facilitates the correlation of miRNA studies between species. Like other small RNAs such as small interfering RNAs (siRNAs) or Piwi-interacting RNAs (piRNAs), miRNAs have important roles in gene regulation and RNA silencing, however miRNAs differ from other small RNAs in their biogenesis (Bartel, 2009).

In 2007, the pioneer study by Bai and collaborators suggested the implication of miRNAs in the development and/or maintenance of inflammatory pain (Bai, Ambalavanar, Wei, & Dessem, 2007). Hence, they showed that upon inflammatory pain initiation by complete Freund's adjuvant (CFA) injection in the masseter muscle multiple miRNAs were down-regulated in the trigeminal ganglion. Then, many others miRNAs have been described as regulators of pain in most, if not all, pain models such as sciatic nerve ligation (Kusuda et al., 2011), diabetic neuropathy (Chattopadhyay, Zhou, Hao, Mata, & Fink, 2012; Gong et al., 2015) or chronic constriction injury (Brandenburger et al., 2012; Genda et al., 2013).

In this review, we focus on the regulatory mechanisms of miRNAs in chronic pain highlighting their potential as therapeutic targets and diagnosis tools.

2. The miRNA system

2.1. miRNAs biogenesis

Half of miRNA-coding genes reside in the intergenic space and are regulated by their own promoters (Corcoran et al., 2009; Lagos-Quintana, Rauhut, Lendeckel, & Tuschl, 2001), around 40% of miRNA genes are situated in introns (Rodriguez, Griffiths-Jones, Ashurst, & Bradley, 2004; Smalheiser, 2008) and the final 10% are located in exon terminals. As a consequence, the expression of half of the miRNA genes depends on the regulation of their host gene, so they may be involved in the control of genetic networks related to the expected function of the host gene product (O'Carroll & Schaefer, 2013). An interesting feature is that many miRNA genes are grouped within clusters, with an intergenic distance ranging from 0.1 to 50 kb, and thus exhibit a similar expression pattern (Baskerville & Bartel, 2005). In addition, miRNAs within clusters are often, but not always, related to each other, while miRNAs from the same family are occasionally clustered (Lagos-Quintana et al., 2001; Lau, Lim, Weinstein, & Bartel, 2001).

miRNAs are transcribed into a primary-miRNA (pri-miRNA) mainly by RNA polymerase II (Lee et al., 2004) but can also be transcribed by RNA polymerase III (Chen, 2004). This pri-miRNA is a large stem-loop structure with a 5′ cap and a poly (A) tail (Cai, Hagedorn, & Cullen, 2004; Lee et al., 2004) recognized by the ribonuclease Drosha, the RNA-binding protein DGCR8 and other auxiliary factors (Han et al., 2004). Then, the pri-miRNA is cleaved by Drosha (RNase III endonuclease) producing a 60–70 nt stem loop intermediate known as pre-miRNA (Denli, Tops, Plasterk, Ketting, & Hannon, 2004; Gregory et al., 2004; Lee et al., 2003; Zeng & Cullen, 2003). This pre-miRNA is actively transported from the nucleus to the cytoplasm by Ran-GTP and Exportin-5 (Lund, Guttinger, Calado, Dahlberg, & Kutay, 2004; Yi, Qin, Macara, & Cullen, 2003). Once there, it is further processed by Dicer, a RNase III endonuclease that cleaves the terminal base pairs and the loop of the pre-miRNA, leaving an imperfectly matching duplex. At this stage, only one strand is finally incorporated into the RNA-induced silencing complex (RISC), the "guide" strand, whereas the other strand called "the passenger" (also called the miRNA* strand) is likely degraded. The criteria defining which of the two strands is loaded into the RISC still need to be clarified but it appears that, in most of the cases, it is the one whose 5′ end is less tightly paired (Khvorova, Reynolds, & Jayasena, 2003; Schwarz et al., 2003).

In addition to the above canonical miRNA biogenesis, there is also a Drosha/DGCR8 independent pathway in which miRNAs are processed from the intron of protein-coding gene by the pre-mRNA splicing machinery (Berezikov, Chung, Willis, Cuppen, & Lai, 2007; Okamura, Hagen, Duan, Tyler, & Lai, 2007; Ruby, Jan, & Bartel, 2007). The expression of these miRNAs, called miRtrons, is linked to the expression of the host gene because they lie in splice site junctions (Isik, Korswagen, & Berezikov, 2010; Ramalingam et al., 2014). MiRtrons are then exported to the cytoplasm and processed by Dicer.

2.2. miRNA mode of action

The mechanism of inhibition by miRNAs is a complex network of interactions between miRNAs and mRNAs. Indeed, one single miRNA can target multiple genes but at the same time, one gene can be targeted by multiple miRNAs (Peter, 2010). These interactions are possible thanks to the modality of hybridization between the miRNA sequence and a