Review Article

MicroRNA-based therapy in pain medicine: Current progress and future prospects

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ABSTRACT

MicroRNAs (miRNAs) are small noncoding RNA molecules of 18–25 nucleotides in length that regulate gene expression involved in fundamental cell processes. The induction and chronicification of pain is associated with many expressional changes in pain-related proteins. miRNA has the potential to regulate gene and protein expression associated with the induction and chronicification of pain. Thus, miRNAs might have promise in therapy and as a diagnostic and prognostic biomarker in pain medicine. The application of miRNA has been an emerging field in pain research in recent years. Many studies focusing on the regulation of miRNAs under different tissue and nociceptive stimuli have been performed in recent years. In this review, we intend to introduce the most recent research in the field of miRNA related with pain medicine such as the expression and function of miRNA in different animal pain model, the challenge of application and delivery of miRNA in vivo, the potential toxic effects of miRNA and future problems in clinical application that need to be resolved. This review focuses on the results of miRNA in animal studies and the prospect for future success.

1. Introduction

RNA interference is a post-transcriptional gene regulating mechanism by small double-stranded RNAs, small interfering RNAs (siRNAs), and microRNAs (miRNAs, miRs). miRNAs are small non-coding RNAs of 18–25 nucleotides that regulate gene expression involved in cell development, differentiation, and proliferation.1 Each miRNA has the potential to target many genes.2–5 An estimated 60% of mRNAs are predicted to interact with more than one miRNA.2–5 The 3′ untranslated region (UTR) of a single gene is predicted to be targeted by several different miRNAs with bioinformatical analysis.2,3 The ability of miRNAs to work together to regulate gene expression has also been proved by experiment.6 As the pathophysiological change of pain is associated with changes of expression in pain-related proteins, miRNAs might be a promising tool to manage inflammatory and neuropathic pain by modulating the expression of gene and protein involved in pain processing pathways. In the past years, siRNAs have already been applied in many pain studies,7 and miRNAs are a rising field in pain research. Therefore, we will review and summarize the recent findings on miRNAs in pain research and discuss whether they could be a potential target for pain management.

2. The mechanism of miRNA biogenesis

miRNAs are mostly transcribed as primary transcripts of long primary miRNAs from intragenic or intergenic regions by RNA polymerase II (Fig. 1).8 The primary transcripts are further processed by Drosha ribonuclease in the nucleus into a hairpin intermediate of about 70–100 nucleotides, called pre-miRNA.9 The pre-miRNA is then transported out of the nucleus to the cytoplasm by exportin 5.10 The pre-miRNAs are then processed by another ribonuclease called Dicer into a mature double-stranded miRNA of about 18–25 nucleotides in the cytoplasm.11 The guide strand or mature miRNA is incorporated into an RNA-induced silencing complex, which separates the miRNA duplex as single strand with sequence complementary to specific target mRNA. With perfect base pairing between miRNA and mRNA, the mRNA is commonly degraded.

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miRNAs with imperfect complementarity to miRNA usually bind to the 3' UTR of mRNA and inhibit translation of miRNA. The RNA-induced silencing complex is the effector complex of the miRNA pathway and is comprised of miRNA, argonaute proteins (argoinduced silencing complex is the effector complex of the miRNA pathway and is comprised of miRNA, argonaute proteins (argonaute 1–4), and other protein factors. Argonaute proteins have a crucial role in miRNA biogenesis, maturation, and miRNA effector functions.

3. Challenges and considerations in the application and delivery of miRNA

There are two main strategies to target miRNA expression in pain treatment. Direct strategies involve the use of oligonucleotides or virus-based constructs to either block the over-expression of miRNA or to substitute for the loss of expression of miRNA. The indirect strategy involves the use of drugs to modulate miRNA expression by targeting their transcription and their processing. To overexpress miRNAs, miRNA mimics can be applied as precursor or as mature miRNA sequences. miRNA inhibitors comprise anti-sense oligonucleotides (anti-miRNAs), miRNA sponges, or miRNA decoys. Antisense oligonucleotides work as competitive inhibitors of miRNAs by annealing to the mature miRNA guide strand and inducing degradation or stoichiometric duplex formation. "miRNA sponges" are longer RNA molecules able to inhibit several miRNAs simultaneously. Several databases such as TargetScan, MiRWalk, miRanda, PICTAR5, and network analysis using Ingenuity Software Analysis have been used to analyze the potential target gene of miRNA.

The blood–brain barrier, a natural barrier hindering the access of miRNA to the central nervous system, is a major challenge for delivery of miRNA into the central nervous system. Some successful approaches for gene silencing in the central nervous system have been reported such as stereotaxic surgery, use of viral vectors, and transgenic constructions. The addition of cholesterol molecule to the sense strand, making the molecule lipophilic, binding high-density lipoprotein, successfully targeting tissues with high-density lipoprotein receptors such as oligodendrocytes in the brain has been reported. Another reported specific approach is the immunoliposome, a complex of a receptor-directed monoclonal antibody, liposome, and the studied molecule. Delivery with immunoliposome enables the conjugated siRNA to cross the blood–brain barrier and reach specific regions of the brain. A similar approach with PEGylated immunoliposomes coated with an antibody against receptors for insulin and/or transferrin for delivering siRNA to the brain in mice has also been reported.

Delivery of miRNA-specific oligonucleotides constitutes another obstacle for their in vivo application. Although miRNAs are highly stable in vivo and show long-lasting efficacy due to a relatively high resistance against nucleolytic degradation compared with mRNA. Several chemical modifications are necessary to prolong half-life in vivo, such as use of deoxyribonucleotides in the duplex overhangs giving greater resistance to nucleases. The use of locked-nucleic acids (LNA, instead of RNA) and adding phosphorothioate linkages in selected positions or substitution of the 2'-ribose at certain positions for 2'-fluoropyrimidines also increases resistance to nucleases. It has also been reported that a single 2'-O-methyl group on the passenger strand of a siRNA duplex can prevent toxicity due to the activation of type I interferon pathway gene expression and hinder Toll-like receptor activation.

4. Development and activity-dependent regulation of miRNAs in pain processing

After tissue injury, changes in many transmitters, ionic channels, and proteins contribute to the development of central and peripheral sensitization which is considered as the cause of chronic pain. Because miRNAs are involved in the regulation of protein and gene expression, it is possible that they also play a role in pain processing pathways. For example, Vo et al reported that miR132 was identified as a target of the transcription factor, CAMP-response element binding protein. miR132 is enriched in neurons and is highly induced by neurotrophins. Expression of miR132 in cortical neurons induced neurite outgrowth. Conversely, inhibition of miR132 function attenuated neuronal outgrowth. miR132 regulates neuronal morphogenesis by decreasing levels of the GTPase-activating protein, p250GAP, which interacts with the glutamate receptor NR2A/B subunits, PSD-95 and β-catenin. Thus, it is possible that miR132 plays a role in memory consolidation and long-term neuronal plasticity.

Wibrand et al examined miRNA expression during long-term potentiation in the dentate gyrus by high-frequency stimulation, which induces transcription of miR-132/212 that is metabotropic glutamate receptor dependent and functionally not correlated with long-term potentiation. By contrast, N-methyl-D-aspartate (NMDA) receptor activation selectively downregulates mature miR-132, miR-212, and miR-219 levels, indicating accelerated decay of these mature miRNAs. Recently, in primary hippocampal neuron cultures, Spronsen et al demonstrated that 51 miRNAs, including miR-134, miR-146, miR-181, miR-185, miR-191, and miR-200a, show altered patterns of expression after NMDA receptor-dependent plasticity, and 31 miRNAs, including miR-107, miR-
134, miR-470, and miR-546 were upregulated by homeostatic plasticity protocols. Their results indicate that specific miRNA expression profiles correlate with changes in neuronal development and neuronal activity. These studies indicate that identification and characterization of miRNA targets may elucidate translational control mechanisms involved in neuron development, differentiation, and activity-dependent pain processing.

5. miRNAs in inflammatory and neuropathic pain

The analysis and validation of miRNAs in different tissue and pain conditions have been reported in many papers (Table 1). Bai et al. first report the downregulation of miRNAs in ipsilateral trigeminal ganglion neurons following inflammatory muscle pain. In this study, selective miRNAs (miR-10a, miR-29a, miR-98, miR-99a, miR-124a, miR-134, and miR-183) were differentially and significantly upregulated in ipsilateral trigeminal ganglion neurons after complete Freund’s adjuvant (CFA)-induced muscle pain. The downregulation of specific miRNAs was considered to enhance the expression of proinflammatory and pronociceptive proteins and thereby facilitate the development of inflammation and allodynia. For studying the nociception-induced dysregulation of miRNA in the prefrontal cortex, miR-155 and miR-223 were upregulated in the ipsilateral and contralateral prefrontal cortex in facial carrageenan-induced inflammation. The potential targets of the two miRNAs—c/EBPβ and granulocyte colony-stimulating factor—were also studied. Significantly downregulated c/EBPβ but upregulated granulocyte colony-stimulating factor were found in the prefrontal cortex of facial carrageenan treated mice. It is postulated that this could lead to increased inflammation and activation of the prefrontal cortex. To examine the role of small RNAs in peripheral pain pathways, Zhao et al. deleted the enzyme Dicer in mouse postmitotic damage-sensing neurons. Deletion of Dicer, an essential enzyme for the generation of mature miRNAs, led to diminished expression of calmodulin-dependent protein kinase II and sodium channel Nav1.8. Inflammatory pain and the number of c-FOS positive neuron in the spinal cord were also attenuated and abolished. However, the deletion of Dicer left the Aβ- and C-fiber mediated pain transmission of the acute nociception unaffected. These results indicate that miRNAs are involved in modulating pain thresholds in inflammatory pain and possibly with therapeutic impact.

In a model of spinal nerve ligation, expression of miRNAs-96, miR-182, and miR-183 are downregulated in ipsilateral dorsal root ganglia (DRG) in rats. The change suggested that altered miRNA expression is a response to nerve injury and is functionally involved in the development and maintenance of neuropathic pain. With the same model of spinal nerve model, Schack et al. performed a miRNA expression profiling study of DRG tissue from rats 4 weeks post-sciatic-nerve ligation revealed significant change in the expression of 63 miRNAs. Of these, 59 were downregulated in the ipsilateral L4 DRG, not the injured L5 DRG, suggesting that miRNA changes in the uninjured afferents may underlie the development and maintenance of neuropathic pain.

Surprisingly, Brandenburg et al. characterized the specific expression pattern of miRNAs in the rat spinal cord in the chronic constriction injury (CCI) model of neuropathic pain in rats. This study further evaluated the time-dependent changes in expression patterns of spinal miRNAs. With miRNA array analysis, only minor changes were observed in miRNA expression levels in the rat spinal cord induced by CCI. Further validation of minor changes in expression levels of miRNAs by real-time quantitative PCR, the relative expression levels of miR-30b, miR-100, miR-10a, miR-99a, and miR-720 were not significantly altered at the investigated time points after CCI to the sciatic nerve. Because induction of neuropathic pain by CCI did not lead to relevant differences in spinal miRNA expression levels at any studied time point, the authors summarized that modulation of miRNAs does not seem to contribute significantly to the changes in gene expression in the spinal cord in this model of chronic neuropathic pain. However, in Genda et al’s study, 111 miRNAs were significantly regulated in CCI rats in both the Day 7 and Day 14 groups compared with sham rats in both groups. Of these 111, there were 75 miRNAs (67.6%) that had been analyzed in previous reports. Certain miRNAs (miR-500, miR-221, and miR-21) were reported to be related to neuropathic pain. Thus, significant change was noted in the expression levels of a large number of miRNAs in the dorsal horn of the spinal cord in CCI rats. Kusuda et al. were able to show that miR-1, miR-16, and miR-206 are differentially regulated in DRGs after induction of acute, inflammatory, and neuropathic pain in mice, whereas in the spinal cord dorsal horn the same miRNAs were regulated only in inflammatory pain, but not in neuropathic or acute pain. The discrepancy in miRNA expression independent pain models shown in these studies suggests that the expression of miRNAs is stimulus-specific.

Apart from profiling of miRNAs in different pain conditions, validation of a single specific miRNA function is a more promising approach to the treatment of inflammatory and neuropathic pain. Among the miRNAs dysregulated in the DRG, miR-21 expression is consistently shown to increase after multiple types of peripheral nerve injury. In Sakai and Suzuki’s study, both mechanical allodynia and thermal hyperalgesia in the neuropathic pain were attenuated by intrathecal administration of miR-21 inhibitor after ligation of the left fifth lumbar spinal nerve. miR-21 is specifically upregulated in the injured DRG neurons and causally involved in the late phase of neuropathic pain. The study performed by Kynast et al. focused on the regulation and function of miR-124a in the spinal cord of mice in a formalin model of inflammatory nociception. miR-124a is constitutively expressed in the spinal cord of mice, particularly in neurons of the dorsal horn and is significantly downregulated by formalin-induced inflammation. Knock-down of miR-124a by intravenous administration of a specific miR-124a inhibitor increased the nociceptive behavior associated with an upregulation of the pain-relevant miR-124a target MeCP2 and proinflammatory marker genes. By contrast, administration of a miR-124a mimic counteracted these effects and decreased nociception. Conclusively, the data indicate that miR-124a is involved in

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inflammatory nociception by regulation of relevant target proteins. In animal models of peripheral inflammation (injection of CFA) and nerve damage (transsection of the sciatic nerve), Tam et al. found that expression levels of miR-143 were significant lower in DRGs ipsilateral to CFA injection but not in nerve damage. Expression levels of miR-143 were also significantly higher in isolectin B4 (I-B4) binding sensory neurons compared with the I-B4 negative neurons. The results demonstrate for the first time that miR-143 is expressed in nociceptive neurons. miR-143 could selectively contribute to mRNA regulation in specific populations of nociceptors. A recent functional study showed that miR-103 is downregulated in neuropathic animals and that intrathecal applications of miR-103 successfully relieve pain. Upregulation of CaV1.2-comprising L-type calcium channel in spinal dorsal horn has a crucial role in chronic neuropathic pain. miR-103 simultaneously regulates the expression of the three subunits forming CaV1.2-comprising L-type calcium channel upon relieving pain.

Several studies examining the analgesic effect of miRNAs on skin or muscle have been reported. miR-203 is known to be involved in keratinocyte growth, differentiation, and skin inflammation. Sun et al. reported that levels of miR-203 were strongly downregulated in keratinocytes after incision. Phospholipase A2 activating protein 1 (LPA1) is a candidate for regulation by miR-203. The authors observed that a miR-203 mimic molecule could block the substance P-induced increase in phospholipase A2 activating protein expression in the rat epidermal keratinocyte cell line. The authors provided evidence for a novel mechanism as contributing to incisional pain, but do not suggest that it could be entirely responsible for incisional pain. Similarly, exploring the analgesic effect on peripheral nervous system, Ikeuchi et al. reported that intramuscular injection of miRNA targeting acid-sensing ion channel 3 could relieve the mechanical hyperalgesia in muscle and paw in the carrageenan-induced muscle inflammation. Pain is a common complication of diabetic neuropathy that, despite substantial advances in understanding of pathophysiology, remains relatively refractory to treatment with available agents. Significant increases in the amount of voltage gated sodium channel isoforms NaV1.7 and NaV1.3 protein in the DRG of rats with streptozotocin-induced diabetes have been demonstrated. To examine the role of NaVz subunit levels in DRG in the pathogenesis of pain in diabetic neuropathy, Chatropadhyay et al. constructed a nonreplicating herpes simplex virus-based vector expressing a miRNA against NaVz subunits. The data revealed subcutaneous inoculation of the miRNA-expressing herpes simplex virus vector into the feet of diabetic rats to transduce DRG resulted in a reduction in NaVz subunit levels in DRG neurons and a reduction in cold allodynia, thermal hyperalgesia, and mechanical hyperalgesia. The results elucidate the role of increased NaVz protein in DRG in the pathogenesis of pain in diabetic neuropathy.

miRNAs have also been reported to be involved in the development of opioid tolerance. Employing bioinformatics, He et al. identified a let-7 binding site in the 3′-UTR of μ-opioid receptor (MOR1) mRNA and confirmed it as a direct target of let-7 in their study. The repressive regulation of MOR by let-7 was revealed in SH-SYSY cells. Conversely, morphine significantly upregulated let-7 expression in SH-SYSY cells and in a mouse model of opioid tolerance. The LNA-let-7 inhibitor decreased brain let-7 levels and partially attenuated opioid antinociceptive tolerance in mice. Let-7 was further identified as a mediator translocating and sequestering MOR mRNA to P-bodies, leading to translation repression. The data suggests that let-7 plays an integral role in opioid tolerance. Based on in silico analysis, an exact match to the seed sequence of miR-134 was found in the 3′-UTR of MOR1. Using CFA-induced chronic inflammatory pain model, Ni et al. investigated the expression profiles of miR-134 and MOR1 in rat DRG. Their result revealed that miR-134 expression level was inversely related to MOR1 expression. These data suggested a model that miR-134 participated in CFA-induced inflammatory pain by balancing the expression of MOR1 in DRGs.

6. Transcriptional gene silencing

RNA-directed DNA methylation is another interesting phenomenon triggered by RNA duplexes which lead to the methylation of the gene promoter region and result in transcriptional gene silencing. siRNA-mediated transcriptional gene silencing was first reported in human cells by Morris et al. in 2004. Recently, another study revealed repressed miR-206b and miR-429 in NMDA1 positive neurons of the nucleus accumbens is associated with an upregulation of the predicted miR-200b/miR-429 target DNA-methyltransferase 3a (DNMT3a) 7 days after sciatic nerve ligation. It is well recognized that DNMT3a is an important DNA methyltransferase that is expressed in postmitotic neurons. DNA methylation can induce long-term transcriptional silencing by directly interfering with transcription factor binding. The results provide new insight into an epigenetic modification that is accompanied by a dramatic decrease in miR200b and miR429 under a neuropathic pain. These phenomena may result in an increase in DNMT3a under neuropathic pain, which leads to the long-term transcription-silencing of several genes. In neuroscience research, RNA-directed DNA methylation might promote a permanent effect, making unnecessary the repetitive siRNAs administrations.

7. miRNAs in visceral pain

miRNA functions have also been investigated in animal models of chronic pelvic pain including of bladder pain syndrome (BPS) and irritable bowel syndrome (IBS). Sengupta et al. recently examined the hypothesis that long-term hypersensitivity in neonatal zymosan-induced cystitis is due to miRNA-mediated post-transcriptional suppression of the developing spinal GABAergic system. Cystitis was produced by intravesicular injection of zymosan into the bladder during postnatal days. Significant upregulation of mature miR-181a in the L6–S1 spinal dorsal horns was found in zymosan-treated rats. The target gene analysis demonstrated multiple complementary binding sites in miR-181a for the GABA receptor subunit GABAAs-1 gene. An increase in miR-181a concomitantly resulted in a significant downregulation of GABA As-1 receptor subunit gene and protein expression in adult spinal cords from rats with neonatal cystitis. It is suggested that this change in spinal cord contributes to the long term sensitization of pain processing in patients with chronic pelvic pain. Using cell-based models, Sanchez et al. showed that prolonged exposure of neurokinin (NK)1 receptor to substance P caused a decrease of NK1 receptor mRNA levels and a concomitant increase of regulatory miRNAs miR-449b and miR-500. In the biopsies of BPS patients, the same miRNAs were significantly increased, suggesting that BPS promotes an attenuation of NK1 receptor synthesis via activation of specific miRNAs. Finally, the authors identified 31 differentially expressed miRNAs in BPS patients and demonstrated a direct correlation between miR-449b, miR-500, miR-328, and miR-320 and a downregulation of NK1 receptor mRNA and/or protein levels. De- fects in urothelial integrity resulting in leakage and activation of underlying sensory nerves are possible causative factors of bladder pain syndrome. Monastyrskaya et al. highlight a possible link between miR-199a-5p expression and the control of urothelial permeability in bladder pain syndrome. Upregulation of miR-199a-5p and concomitant downregulation of its multiple targets might determine the impact of a tight urothelial barrier, leading to chronic bladder pain syndrome. In IBS patients with increased intestinal permeability, the urothelium is considered to be less intact, allowing increased bacterial and/or bacterial products to enter the blood stream. These products may then reach the central nervous system and trigger a pain response. The authors of this study hypothesized that by targeting the urothelial barrier, miR-199a-5p expression may be upregulated, leading to a decrease in pain sensation. This hypothesis was supported by the findings that miR-199a-5p expression was increased in IBS patients compared to healthy controls. The authors also found that miR-199a-5p expression was inversely correlated with pain scores, suggesting that increased miR-199a-5p expression may be associated with decreased pain perception. Overall, this study provides evidence for a role of miRNAs in the regulation of pain in patients with chronic pelvic pain and suggests that targeting miR-199a-5p may be a potential therapeutic strategy for the treatment of this condition. However, further research is needed to confirm these findings and to fully understand the role of miRNAs in bladder pain syndrome.
membrane permeability, increased expression of miR-29a was found in blood microvessicles, small bowel, and colon tissues. miR-29a has a complementary site in the 3′-UTRs of the glutamate-ammonia ligase gene that leads to decreased glutamine synthetase levels, increased intestinal permeability and chronic visceral pain in IBS patients. Suppressing the expression of miR-29a in vitro will restore intestinal permeability.\(^54\)

In summary, these studies indicate that miRNAs are involved in the onset and progression of neural sensitization and play an important role in inflammatory, neuropathic and visceral nociception. Therefore, these studies provided targets for miRNAs for treatment of inflammatory, neuropathic, and visceral pain.

8. Potential side effects

As discussed above, proper delivery and appropriate stability are two major concerns for in vivo delivery of miRNAs. Development of viral vectors/polypeptides and chemical modifications are expected to overcome such hurdles in the application of RNA interference in neurological application. Except for the problems of delivery and stability, the major difficulty in application of miRNAs is their off-target effects. miRNAs regulate many genes, the potential off-target effects of miRNA may produce toxic phenotypes,\(^55,56\) e.g., T helper 1 cell responses of immune reaction.\(^57\) These problems could be solved by designing and constructing effective systems that deliver the synthetic miRNA specifically to target genes in the cells. The activation of that immune system is also a potential side effect: an increased activation of immune mechanisms that are stimulated by small molecules similar to viral defense pathways.\(^58\)

9. Conclusions

In recent years, miRNAs have gained increasing interest as research tools, biomarkers, and as a potential new treatment of pain. Many studies focusing on the regulation of miRNAs under different tissue and nociceptive stimulus have been performed. In the near future, a trend toward studying the expression and function of a single specific miRNA and its target genes can be observed. Understanding the distinct roles of a single miRNA in diverse pain conditions and tissue types will be one of the great challenges in the future. The recent research of application of miRNAs in pain medicine have demonstrated early promise in the treatment of pain. However, challenges with respect to the use of miRNA-based therapeutics such as poor cellular uptake or a low bioavailability as well as off-target effects or long-term safety concerns in humans remain to be further explored. Therefore, the future prospects of miRNA-based treatment will require further adjustments to maximize miRNAs potency while minimizing off target toxicity and immunogenicity.

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