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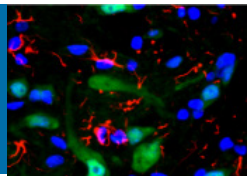

Review

Advances and progress of MicroRNA in DRG neurons

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Abstract: MicroRNAs (miRNAs or miRs), a group of small non-coding RNAs, can down-regulate specific genes expression by binding to the target mRNA to interfere with many cellular functions including proliferation, differentiation, development and apoptosis. Recent studies have showed that microRNA also plays an important role in the development and progression of pain. The roles of miRNAs in the regulation of responses of DRG neurons to injury stimuli, however, are not fully understood. Here, a review is formed based on the expression and role of microRNA in dorsal root ganglion neurons in different pain models.

Key words: MicroRNAs; Dorsal root ganglion; Neuron; Pain edema

Introduction

As the primary afferent neurons of pain, dorsal root ganglion neurons play important roles in the peripheral mechanism of pain. DRG neurons contain not only nociceptive neurotransmitters and neuromodulators, such as tachykinin, excitatory amino acids, but also contain modulators of presynaptic receptor, such as γ-aminobutyric acid, opioids and purine, as well as some ion channels. MicroRNA cannot be translated into proteins, except regulate their metabolism, which major involved in the regulation of post-transcriptional gene by targeting special mRNA molecule. Chip, qPCR and in situ hybridization methods confirmed the presence of a group of injuries regulated miRNAs, supports miRNA pathway plays a regulatory role in peripheral nerve regeneration process (Wu D, et al., 2011). Wu D and other researchers confirmed several key miRNA biosynthetic enzymes expressed in sciatic nerve injury model and cultured DRG axons. Under the knockout of Dicer, axonal regeneration and functional recovery of anatomy and physiology are impeded (Wu D, et al., 2012), which suggest that complete Dicer dependent miRNA pathway is required in the regeneration of injured peripheral nerve. And microRNA expression in different pain models and different organizations is different in time and space.

Effect of microRNA on DRG neurons in anesthesia toxicity

Local anesthesia with bupivacaine can suppress neurite outgrowth and promote apoptosis in mouse DRG neurons, simultaneously, reduced the expression of microRNA 26a (miR-26a) gene. To the contrary, up-regulated miR-26a promotes neurite outgrowth and reduces apoptosis in bupivacaine-injured DRG neurons. Luciferase assay and western blot confirmed that phosphatase and tensin homolog (PTEN) was down-stream target of miR-26a in DRG neurons. Up-regulating miR-26a to suppress PTEN signaling pathway may be an effective method to protect local anesthetic-induced nerve injury in spinal cord (Cui C, et al., 2015). Further studies showed MiR-210, through the regulation of BDNF, plays important role in anesthetics-induced DRG neurotoxicity. Within the initial 24 h after bupivacaine treatment, miR-210 was constantly upregulated, whereas, application of miR-210 inhibitor efficiently down-regulated

Article history: Received: 28 January 2021 Revised: 15 February 2021 Accepted: 9 Mar 2021 Published: 28 Mar 2021

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endogenous miR-210, protected apoptosis and neurite retraction in bupivacaine damaged DRG neurons (Wang Y, et al., 2015).

MicroRNA expression in DRG with sciatic nerve injury

Microarray profiling indicated that 13 miRNAs were differentially expressed in rat DRGs (L4-L6) during the initial 7d period post sciatic nerve transection, and the expressions of miR-21 and miR-222 were continually increased over the time period. Over-expression of miR-21 and miR-222 inhibited cell apoptosis and enhanced cell viability in cultured DRG neurons. Tissue inhibitor of metalloproteinase 3 (TIMP3), a pro-apoptotic protein in various cancer cells, was identified as a common target of miR-21 and miR-222. All the results showed that miR-21 and miR-222 inhibited neuronal apoptosis at least partially through suppressing TIMP3 after peripheral nerve injury (Zhou S, et al., 2015).

MicroRNAs are involved in modulation of neural cells after peripheral nerve injury

Strickland IT et al. also detected changes in 20 transcripts of miRNAs in L4 and L5 dorsal root expression after sciatic nerve transection ganglion, and miR-21 was up-regulated by 7-fold in the DRG, 7 days after axotomy. MiR-21 up-regulated could promote neurite outgrowth in dissociated rat DRG, and directly down-regulate expression of sprout 2 protein determined by western blot analysis and 3' untranslated region (UTR) luciferase assays (Strickland IT, et al., 2011). Zhou S et al. also showed 26 kinds of known miRNAs exhibited time dependent changes after sciatic nerve transection 0, 1, 4, 7 and 14 d in the L4-L6 DRGs by miRNAs chip. MiR-222 up-regulated promote neurite outgrowth, while it silenced by inhibitor can reduce neurite growth. And further knockdown experiments confirmed its direct target in DRG neurons is phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a major inhibitor of nerve regeneration. Collectively, miR-222 might regulate the phosphorylation of cAMP response element binding protein (CREB) through PTEN, and c-Jun activation might enhance the miR-222 expression to regulate neurite outgrowth (Zhou S, et al., 2012). MiR-21 is an axotomy-induced miRNA that enhance axon growth, and suggest that miRNAs are important players in regulating growth pathways following peripheral nerve injury. And find potential targets related to nerve regeneration through bioinformatic analysis. MiR-222 could regulate neurite outgrowth from DRG neurons by targeting PTEN. MiR-132, highly expressed on axons, knockdown reduced extension of cultured DRG axons, whereas overexpression increased extension. In the cut axons, miR-132 regulates Rasal (Ras GTPase activator) translation. MiR-132 expression in DRGs peaked in the period of maximum axon growth in vivo, consistent with its effect on axon growth, and suggesting a role as a developmental timer (Hancock ML, et al., 2014).

MiR-144, 145 and 214 were located in primary sensory neurons confirmed by in situ hybridization analysis, which were down-regulated after sciatic nerve transection. Robo2 and srGAP2 are the targets of miR-145 and miR-214. In cultured neurons, miR-145 inhibits axon growth through down-regulating Robo2. MiRNAs can mediate regeneration following injury associated with Slit-Robo-srGAP signal pathway (Zhang HY, et al., 2011).

Collectively, following sciatic nerve injury, miR-21, -222, -132 were up-regulated and as positively regulators on axonal growth respectively through their target genes TIMP3, PTEN and Rasal; contrast to miR-144,-145,-214, which were down-regulated and mediated the regeneration process after injury through Slit-Robo-srGAP pathway.

Expression of microRNA in chronic neuropathic pain

Norcini M et al. distinguished several miRs associated with chronic neuropathic pain through two different spared nerve injury (SNI) models: Sural-SNI and Tibial–SNI with various pain phenotypes. Both models induced strong mechanical allodynia, but only Sural-SNI rats maintained strong mechanical and cold allodynia, the same as previously reported. In contrast, Tibial-SNI rats recovered from mechanical allodynia and never developed cold allodynia. 7 miRs expressing in L3-L5 DRG, are high expressed in Tibial-SNI, and lower expressed in Sural-SNI, even four of them lower than sham group. Bioinformatics analysis showed that these miRs could affect the expression of some ion channels, and the increased 7 miRs may contribute to the recovery from neuropathic pain, whereas the decreased 4 miRs associated with attenuating neuropathic pain (Norcini M, et al., 2014).

Chen HP et al. found that miR-96 could relieve neuropathic pain induced by condition chronic constriction sciatic nerve injury (CCI) model. MiR-96 expression was decreased in the ipsilateral DRG after peripheral nerve injury, while Nav1.3 was increased. Administration of miR-96 by intrathecal injection can inhibit the expression of Nav1.3 induced by the CCI. Also, miR-96 can inhibit the expression of Nav1.3 mRNA in cultured DRG neurons. So, miR-96 can take part in the regulation of neuropathic pain induced by CCI maybe through inhibiting the expression of Nav1.3 (Chen HP, et al., 2014).

Studies also found that miR-21 is sustained up-regulation in DRG after peripheral nerve injury. Following ligation of the specific L5 spinal nerve (SNL), miR-21 is sustained increase in injured DRG neurons, rather than in the DRG neurons around the injury. The expression of miR-21 also can be increased by administration of IL-1B through intrathecal in-

jection, while intrathecal injection of miR-21 inhibitors can relieve mechanical pain and thermal pain. Neuropathic pain is closely associated with the specifically up-regulated miR-21 in injured DRG. Therefore, miR-21 and its regulating system can be used as targets for the treatment of chronic neuropathic pain through intrathecal injection (Sakai A, et al., 2013).

Sensory organ-specific microRNAs (miR-96, -182, and -183), highly expressed in adult rat DRG, are significantly reduced in the injured DRG neurons detected by QPCR. The distribution of microRNAs in DRG neurons is corresponding with the changes of stress granule (SG) protein and T-cell intracellular antigen 1 (TIA-1) (Aldrich BT, et al., 2009).

Expressions of miR-96, -182, -183 are significantly reduced, contrast to the increased Nav1.3 in DRG neurons with the occurence of neuropathic pain, while the increased miR 21 plays a role in pain relief.

The function of microRNAs in diabetic peripheral neuropathy

Wang L et al. found that hyperglycemia could down-regulate the expression of miR-146a and up-regulate interleukin- 1 receptor-activated kinase (IRAK1) and tumor necrosis factor using a model of diabetic peripheral neuropathy (BKS.Cg-m+/+ Lep(db)/J(db/db) mice) and cultured DRG. They also found the release of inhibited neurotransmitters (enkephalins and GABA) from DRG mediated by gene transfer can reduce pain-related behavior, which is coinside with the level of Na (V) 1.7 protein (Chattopadhyay M, et al., 2012).

Up-regulated miR-146a can increase the survival of cultured DRG neurons under high glucose conditions, and the level of miR-146a was negative with the level of IRAK1 and receptor-associated factor 6 (TRAF6) in DRG. Sildenafil can increase the expression of miR-146a and decrease the levels of IRAK1 and TRAF6 in the DRG to treat diabetic peripheral neuropathy. Additionally, blocking miR-146a in vitro can terminate the protective effect of sildenafil and down-regulate the protein expressions of IRAK1 and TRAF6 of DRG in hyperglycemia. MiR-146a plays an important role in DRG neurons apoptosis induced by high glucose (Wang L, et al., 2014).

Zhang X and other researchers found the expression of miR-29b was down-regulated after STZ injection, over time, more pronounced reduction, which was associated with higher apoptosis rate and more severe edema of axon. Meanwhile, axonal regeneration gene is suppressed, and neurodegenerative gene is activated, which can be reversed by recovery the expression of miR-29b. The study suggests that miR-29, which can terminate the activation of Smad3, has protective effect on rat DRG with diabet disease (Zhang X, et al., 2014).

Down-regulated miR-146a and miR-29b reduce the inhibition on IRAK1, TNF and Smad3, and promoted apoptosis of neurons.

MicroRNA expression in inflammatory pain model

MiR-143 locates in the cytoplasm of cultured mouse DRG, and higher expresses in isolectin B4 (I-B4) isoform binding sensory neurons contrast to the I-B4 negative neurons by bead enrichment analysis. Combing with the peripheral inflammatory animal model (CFA injection) and nerve injury model (sciatic nerve transection), the expression of miR-143 is significantly decreased in the ipsilateral DRG after nerve injury or CFA injection.MiR-143 higher expressed in the I-B4-positive neurons and decreased in inflammatory conditions, but not decreased in the case of axotomy, can regulate selectively mRNA in different pain condition (Tam Tam S, et al., 2011).

MOR1, a major transcript of μ-opioid receptor (MOR) gene, plays a major role for opioid analgesics, and miR-134 locates in the 3'UTR of MOR1. There was a negative correlation between miR-134 and MOR1 in CFA induced chronic pain models, down-regulated miR-134 and up-regulated MOR1 appear in the same organization with inflammatory pain, showed by qPCR, in situ hybridization, immunohistochemistry and luciferase assay technologies. MOR1 was up-regulated in SH-SY5Y cells following miR-134 suppressed, which suggests MOR1 was the target of miR-134. MiR-134 involved in CFA-induced inflammatory pain by balancing MOR1 expression in DRG, and can be as potential therapeutic target for the treatment of neuropathic and inflammatory pain (Ni J, et al., 2013).

MiR-1 also expresses in DRG neurons, higher expresses in I-B4 negative DRG neurons compared with I-B4 positive ones, and plays a role in the outgrowth of neurite (Bastian I, et al., 2011).

Kusuda R et al. found the mature bodies of miR-1, -16 and -206 were expressed in DRG and spinal cord dorsal horn using qPCR technology. In CFA-induced inflammatory conditions, miRs-1 and -16 significantly reduced in the DRG, however, reduced miR-206 has a time-dependent manner. In contrast, these three miRNAs are up-regulated in the spinal cord dorsal horn. After partial sciatic nerve ligation, miR-1 and -206 were down-regulated in DRG, while there was no change in the dorsal horn of the spinal cord. On the other hand, after neurectomy, miR-1, -16 and 206 were increased in DRG and showed time-dependent manner, however, the expression of miR-1 in the spinal dorsal horn was significantly reduced. Acute toxic stimulation caused by capsaicin can increase the expressions of miR-1, -16 in DRG, while in the dorsal horn of spinal cord only high doses of capsaicin can decrease the expression of miR-206. This study demon-

strated miRNAs on DRG and spinal dorsal horn play different roles in different pain states and their expression in pain system showed specific not only in time and space but also in stimulate dependent (Kusuda R, et al., 2011).

The role of microRNA in osteoarthritis-induced pain

Knee osteoarthritis animal model established by transecting medial meniscus, is employed to assess the relationship between pathological changes and chronic joint pain through behavioral testing, histology and image analysis. MicroRNA microarray found that followed by OA pain, miR-146a and miR-183 were significantly decreased in DRG (L4/L5) and spinal dorsal horn associated with the raised inflammatory media. MiR-146a and miR-183 can effectively relieve OA joint pain, and regenerate cartilage around the knee (Li X, et al., 2013).

MiRNA expression pattern in DRG and muscle tissue after denervation in rats

Denervation model is established using a non-compressible silicone rubber tube following by surgical decompression, to observe microRNA expression changes in neurons and muscle tissue with innervation.

About half of muscle tissue-specific miRNAs, miR-1 and miR-133a are down-regulated 3-6 months after crush injury, by using miRNA microarray and qPCR analysis, while one or three months followed decompressing, the expression of miR-1 and miR-133a did not change or decreased and there was no significantly difference in the expression of miR-206. The various expressions of miRNAs are showed in DRG and innervating muscle in crush neuropathy and denervated injury, and the epigenetic regulation is different (Rau CS, et al., 2010).

Role of extracellular microRNA in the occurrence of pain

Park CK et al. reported that extracellular miRNAs can quickly activate nociceptive neurons through TLR-7 and TRPA1 ion channels. In DRG, miRNA-let-7b induces fast inward currents and action potentials, and requires GUUGUGU motif, which occurs only in neurons co-express TLR7 and TRPA1, while terminated in mice lack of Tlr7 or Trpa1. Over-expressing TLR7/TRPV1 in DRG and HEK293 cells, a rapid spontaneous pain was triggered through TLR7 and TRPA1 after plantar injection of let-7b. After activation of neurons, let-7b is released from DRG, and let-7b inhibitors can reduce formalin-induced TRPA1 currents and spontaneous pain. Secreted extracellular miRNAs can be used as a new medium of pain in nociceptive neurons by activating TLR7/TRPA1 (Park CK, et al., 2014).

MicroRNA and remyelination

Recently, researchers found that microRNAs play an important role in the development of oligodendrocytes, especially miRs-138, -219, -338, and -9 have been used as key factors in regulating oligodendrocyte development from oligodendrocyte precursor cells and other nodes about the formation of mature myelin. Many miRNA studies associated with myelinogenesis from oligodendrocytes have been used in central nervous system diseases (including multiple system sclerosis, ischemic stroke, spinal cord injury and ADLD) (Fitzpatrick JM, et al., 2015).

Viader A and his colleagues found 87 miRNAs were expressed in peripheral nerves of adult mice through miRNA expression profiles analysis on contused sciatic nerve distal end, among them 48 miRNAs exhibited dynamic changes following nerve injury, and most of them took participate in inhibiting Schwann cell differentiation and proliferation. Among of miRNAs expressed in adult mouse SCs cells, miR-34a and miR-140 are the regulators for SCs proliferation, differentiation and forming functional myelination. Wherein miR-34a cooperated with Notch1 and Ccnd1—positive adjustment factors for dedifferentiation and proliferation, to control dynamic changes of SC cycle. In DRG and SCs co-cultured case, miR-140 acts on the transcription factor Egr2 (a major regulator of myelination) to regulate myelin formation. SC miRNAs are the main regulators in schwann cell regeneration after nerve injury (Viader A, et al., 2011).

The repair effect of microRNA after nerve injury

There is only one report associated with microRNA138 and spinal cord injury, which was produced in our lab, we found that MiR-138 could promote neural plasticity by regulating vimentin and play an important role in the treatment of spinal cord injury (Qian BJ, et al., 2015). Another reported that miR-142-3p was a potential therapeutic target for the recovery of sensory function after spinal cord injury (Wang T, et al., 2015).

During in the critical period of development, neural network reconstruction is accompanied by changes of cell populations in the hypothalamus. MicroRNAs play an important role in regulating nerve function, including proliferation of neural stem cells, neuronal migration, maturation and integration into an appropriate loop, by adjusting different mRNA targets. MiR-138 was observed to play a role in cell proliferation and migration in cultured hypothalamus cells with E16-day chicken. Ectopic expression of MiR-138 enhances the migration of hypothalamus cells, but does not affect cell proliferation by inhibiting the expression of Reln (Kisliouk T, et al., 2013).

The impact of microRNA on viral latency

Comparing 15 died individuals with latent herpes virus infection by the immune response found that α herpes virus dormant in the trigeminal ganglia associated with chronic inflammation, while in the dorsal root ganglia without chronic inflammation (Hüfner K, et al., 2006).

Application of siRNA is capable of specifically and effectively silencing the target gene of DRG and spinal cord in different pain models. Replication defective carrier of HSV can be effectively targeted DRG neurons, and be used to express shRNA and miRNA. The expression of HSV-mediated siRNA/miRNA in sensory neurons can last at least a week after a single injection. MiRNAs improve their safety. The use of miRNA-based vectors in sensory neurons can achieve gene silencing and improve their safty (Anesti AM, et al., 2010).

MiR-138, as a neuron-specific microRNA, can inhibit the expression of ICP0 (lytic gene expression of trans-acting factors). After cultured neurons infected with HSV-1 (M138) mutation, miR-138 target site on ICP0mRNA is destroyed, then the expressions of ICP0 and other cleaved proteins are increased. MiR-138, as a neuron factor, can inhibit the expression of HSV-1 lytic gene, promote the host survival and prolong the virus latency (Pan D, et al., 2014).

MiR-H6, a latency-associated micorRNA, cannot influence the establishment of viral latency and recurrence (Tang S, et al., 2011).

Conclusion

The occurrence of pain alters the expression of proteins in DRG, so targeting some of these proteins could lead to successful treatments for sustained pain. MicroRNA majorly involves in the regulation of post-transcriptional genes, which can inhibit the translation of mRNA through complementary matching with 3'untranslated region of the mRNA molecule. During the development of pain, microRNAs play important roles in the process of occurrence or abirritation of pain by acting on the target proteins, whose expression varies in different stage and tissue during the occurrence of pain. To clarify the specific microRNA expression profiling under different pain states, has important clinical significance for the treatment of intractable pain.

Acknowledgements

This project was supported by the Science and Technology Research Program for Colleges and Universities in Shandong Province, China (grant No.J11LF61).

Conflict Interests

No conflict of interest

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MicroRNA 在 DRG 神经元中的研究进展

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[摘要]：MicroRNAs (miRNAs 或 miRs) 是一组小的非编码 RNA，通过与靶基因 mRNA 结合，干扰细胞增殖、分化、发育和凋亡等多种功能，下调特定基因的表达。近年来的研究表明，MicroRNA 在疼痛的发生发展过程中也发挥着重要作用。然而，MicroRNA 在调节 DRG 神经元对损伤刺激的反应中的作用尚不完全清楚。本文对不同疼痛模型中背根神经节神经元中 MicroRNA 的表达及作用进行综述。

[关键词]：MicroRNAs；背根神经节；神经元；疼痛

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