Burdenko's journal of neurosurgery
2020, №4, pp. 104-110
https://doi.org/10.17116/neiro202084041104

Non-coding RNAs as therapeutic targets in spinal cord injury

© O.A. Beylerli[1], Sh.T. Azizova[2], N.A. Konovalov[3], A.D. Akhmedov[3], I.F. Gareev[1], A.A. Belogurov[4]

[1]Bashkir State Medical University of the Ministry of Health of the Russian Federation, Ufa, Russia;
[2]Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia;
[3]Burdenko Neurosurggical Center, Moscow, Russia;
[4]Shemyakin-Ovcinnicov Institute of Bioorganic Chemistry, Moscow, Russia

Abstract

Spinal cord injury (SCI) may be followed by persistent motor dysfunction and somatosensory disturbances that negatively influences the quality of life of patients and creates a significant economic burden. Analysis of secondary biological processes associated with changes in genetic expression is becoming increasingly important every day in understanding the pathophysiology of spinal cord injury. The results of international sequencing of the human genome were analyzed in 2004. These data revealed about 20,000 protein-coding genes covering near 2% of the total genomic sequence. The vast majority of gene transcripts are actually characterized as non-coding RNAs (ncRNAs). These RNA clusters do not encode functional proteins and ensure post-transcriptional regulation of gene expression. The clusters may be small (approximately 20 nucleotides) known as miRNAs or the transcripts can enroll over 200 nucleotides defined as long non-coding RNAs (lncRNAs). Some modern studies describe transient expression of microRNA in case of spinal cord injury. These RNAs are associated with inflammation and apoptosis, functional recovery and regeneration. Large-scale genomic analysis has demonstrated the existence of multiple lncRNAs whose expression is associated with some processes of spinal cord injury. lncRNA can be divided into two categories depending on the position in relation to the coding genes: intergenic and intragenic. Intergenic lncRNAs is currently the most studied class. Intragenic lncRNAs can be subdivided depending on the overlap of the coding genes (antisense, intron, etc.). According to recent studies, long non-coding RNAs are abundantly present in the tissues of central nervous system and may be crucial in the pathogenesis of certain diseases of nervous system. At the cellular level, it has been shown that lncRNAs regulate the expression of protein-coding RNAs. Moreover, these molecules are involved into such processes as neuronal death, demyelination and glia activation. This review is devoted to the role of ncRNAs in the pathogenesis of spinal cord injury and their potential use as targets for the treatment of consequences of spinal cord injury.

Keywords: *ncRNA, miRNA, lncRNA, spinal cord injury, pathophysiology, glial activation, therapy.*

Information about the authors:

Beylerli O.A. — https://orcid.org/0000-0002-6149-5460; e-mail: obeylerli@mail.ru*
Azizova Sh.T. — https://orcid.org/0000-0002-8672-2703
Konovalov N.A. — https://orcid.org/0000-0002-9976-948X
Akhmedov A.D. — https://orcid.org/0000-0001-5780-8519
Gareev I.F. — https://orcid.org/0000-0002-4965-0835
Belogurov A.A. — https://orcid.org/0000-0002-2033-9621
* — corresponding author

To cite this article:

Beylerli OA, Azizova ShT, Konovalov NA, Akhmedov AD, Gareev IF, Belogurov AA. Non-coding RNAs as therapeutic targets in spinal cord injury. *Burdenko's Journal of Neurosurgery = Zhurnal voprosy neirokhirurgii im. N.N. Burdenko.* 2020;84(4):104-110. (In Russ.). https://doi.org/10.17116/neiro202084031104

Abbreviations

SCI — spinal cord injury
ncRNA — non-coding RNA
lncRNA — long non-coding RNA
SC — spinal cord

Traumatic spinal cord injury often results significant impairment in quality of life and disability. It is associated with impairment and loss of motor and sensory functions, impairment of vital function (respiratory, cardiovascular, gastrointestinal and urinary system dysfunction), musculoskeletal deformities [1, 2]. Annual incidence of spinal cord injury worldwide is 10.5 cases per 100,000 (about 750,000 cases annually). Mean age of victims is 39.8 years. SCI incidence in men is 3.37 times higher than in women. Thus, the most active group of population is under risk that makes important the development of new approaches to the diagnosis and treatment of this lesion [2].

There are two main mechanisms of SCI: primary mechanical and secondary one including inflammation, acidosis, apoptosis and glial scar. The last one is a physical and molecular barrier preventing axonal regeneration [3—5]. Secondary SCI includes astrogliosis as significant augmentation of the number of astrocytes in the area of neuronal injury, infection, stroke or neurodegenerative disease. However, astrogliosis is essential in regeneration processes since it restores homeostasis after SCI, facilitates recovery of blood-brain barrier and suppresses inflammation [6, 7]. Favorable effect of astrogliosis was found in early hypertrophic phase after SCI while development of dense scar in late hyperplastic phase impairs axonal regeneration [8, 9]. In addition to neurons, other SC cells, such as oligodendrocytes and microglia cells are subject to apoptosis [6]. Loss of oligodendrocytes in white matter continues throughout several weeks after SCI and can contribute to progressive demyelination [10, 11].

Changes in gene expression are important in pathogenesis of secondary SCI. However, the mechanisms regulating expression of these genes are unclear. About 70—80% of human genome are actively transcribed in RNAs, while only 2% are transcribed in protein-coding microRNAs. Thus, the number of non-coding RNAs (ncRNAs) is much higher than the number of protein-coding genes. Non-coding RNAs are grouped into two main classes depending on transcript dimension: small and long. Small ncRNAs include well-described microRNAs, small interfering RNAs (miRNAs) and PIWI-interacting RNAs. NcRNAs are good candidates for the role of regulators of secondary SCI since these molecules can ensure post-translational regulation of genes [11—13]. Some forms of microRNAs are essential in embryonic development of nervous system and important mediators of neuronal plasticity [14, 15]. A number of microRNAs have been proved to be involved in the development of severe neurological diseases, such as Tourette's syndrome [16]. Some trials are devoted to the role of microRNAs in neurodegeneration processes [17, 18]. Up to 40% of all known ncRNAs are specifically expressed in the brain and other parts of central nervous system [19]. This finding has shown that long non-coding RNA (lncRNA) can participate in pathogenesis of nervous system diseases. Therefore, identifying the expressed ncRNAs by genomic approaches will be valuable to understand the development of ncRNA-mediated diseases. The role of ncRNA in SCI is still unclear although expression of large amount of ncRNA was found in SC of mice.

MicroRNA expression in spinal cord injury

N.K. Liu et al. performed an experiment on rats with traumatic brain injury in order to determine microRNA expression over time [15]. The authors concluded that injured SC in a rat contains approximately 77% (269) of microRNAs identified in a healthy rat (350). Thus, SC is a rich source of microRNA expression. Expression of 97 out of 269 microRNAs changed after SCI. Moderate, high and very high expression of 60 out of 97 microRNAs was found. Expression of other 37 microRNAs was low. SC decompression is preferable surgical treatment of SC trauma. M. Ziu et al. analyzed expression of various microRNAs depending on duration of SC compression [20]. These researchers proved that expression of some microRNAs differs depending on compression time. In particular, miR-107 is expressed in long compression model and does not change in short compression model. Expression of miR-148 is increased in 3 and 6 hours after prolonged compression and after 6 hours in short compression model. It was also shown that miR-210 is expressed after 3, 6 and 24 hours in long compression model and only after 24 hours in short compression model.

MicroRNA associated with inflammation and apoptosis

V. Sahni et al. conducted an experiment on mice with SCI and determined the role of bone morphogenetic proteins (BMPs) and their receptors in secondary astrogliosis after SCI [9]. These authors detected significant augmentation of BMP4 in 4, 7 and 15 days after injury. They also found moderate increase of BMP7 levels in 4 days after injury and normalization 7 days later. The researchers also observed increased transcription of 1a BMP receptor (BMPR1a) and GFAP protein (glial fibrillary acidic protein) in 4 and 7 days after injury. BMP signaling pathway includes SMAD proteins (similar to mothers against decapentaplegic). It was shown that these proteins control posttranscriptional processing of miR-21 [17]. The authors analyzed the behavior of this microRNA and demonstrated that BMPR1a-mediated signal transmission inhibits cytoplasmic processing of miR-21. Thus, final processed product of this microRNA is usually inhibited after SCI. O. Bhalala et al. conducted an experiment on mice in order to clarify the role of miR-21 in astrocytic response after SCI [21]. The authors found that miR-21 overexpression in astrocytes after SCI weakens hypertrophic response. Moreover, they observed that miR-21 inhibition is accompanied by increased axonal density at the site of lesion. The authors revealed a new effect of miR-21 in astrocytic regulation of hypertrophy and glial scar progression after SCI. V. Izumi et al. analyzed miR-

223 and found high expression of this microRNA in 12 hours after SCI [22]. As for apoptosis, G. Liu et al. demonstrated a significant change in expression of some microRNAs in rats with SCI. In fact, they found increased expression of Let-7a and miR-16 and reduced miR-15b level in 10 days after injury [23].

MicroRNA associated with functional recovery and regeneration

Regeneration is a reproduction of accurate copies of lost anatomical structures. This phenomenon is observed in some vertebrate species, such as salamanders, axolotls and danio rerio and lost in mammals. Molecular mechanisms of this process are still unclear [24]. The role of microRNA in SC regeneration after injury was studied in some of these species. T. Sehm et al. conducted an experiment on axolotls and determined the role of miR-196 in tail regeneration after its amputation [24]. The authors found significantly increased expression of miR-196 within 14 days after amputation. Inhibition of miR-196 significantly impaired regeneration. These data indicate that this microRNA is essential at the early stages of regeneration of the tail in axolotls. J.F. Díaz Quiroz et al. found that miR-125b is necessary for functional regeneration after SCI in the same species [25]. The authors have shown that reducing the level of miR-125b in axolotl up to that in rats inhibits regeneration through regulation of the Sema4D gene. The last one causes development of glial scar. Y.M. Yu et al. studied the role of miR-133b in functional recovery after SCI [26]. For this purpose, they used a model of SCI in danio rerio and revealed positive regulation of miR-133b in neurons. Inhibition of miR-133b changed motor recovery and reduced axonal regeneration within the spinal cord slice.

Potential targets of microRNA in spinal cord injury

Inflammation, acidosis and apoptosis

N.K. Liu et al. studied the role of microRNA after SCI in analysis of potential target genes [15]. Statistical analysis demonstrated that these targets are genes encoding the components involved in various physiological processes such as inflammation, acidosis and apoptosis. Genes inhibiting inflammatory process are potential targets for some microRNAs (miR-221, miR-1, miR-206, miR-152, miR-122, miR-181a, miR-411, miR-99a, miR-34a, miR-30c, miR-384-5p, miR-30b-5p and miR-214). A number of genes responsible for apoptosis are potential targets for microRNA. Expression of these microRNAs is reduced after SCI (miR-127, iR-181a, miR-411, miR-34a and miR-384-5p). According to available data, abnormal expression of microRNA after traumatic SCI is essential in secondary damage of the spinal cord. Thus, these microRNAs may be potential targets in SCI management. V. Sahni et al. reported that miR-21 negatively regulates reactive hypertrophy of astrocytes in SCI [9]. However, the authors have not yet been able to identify the targets of miR-21, which can affect astrocyte size enlargement. G.Liu et al. studied microRNA associated with apoptosis and showed that increased expression of Let-7a was accompanied by increased expression of RAS (genes and proteins (so-called small G-proteins (small GTPases))) and MYC (genes regulating cellular proliferation, differentiation and carcinogenesis) in 10 days after lesion. However, expression of RAS and MYC normalized after 31 days although Let-7a level remained elevated [23]. On the one hand, increased expression of microRNA was due to increased expression of Bcl-2. On the other hand, exercise after SCI was shown to be maintaining muscle mass in paralyzed limbs, stimulating anatomical and biochemical plasticity in spinal cord and increasing the level of neurotrophic factors in muscles and spinal cord [27—32]. These data justified a research of the effect of physical exercise on expression of some microRNAs [23]. In this trial, G. Liu et al. showed that exercise within 5 days after SCI was accompanied by significantly increased expression of miR-21 with anti-apoptotic effect and reduced expression of miR-15b [23]. Increased expression of miR-21 resulted decrease in expression of RNA-messenger PTEN (phosphatase and tensin homolog) and PDC4 (programmed cell death protein 4). Inhibition of these proteins is known to be associated with reduced apoptosis in cancer cells through inhibiting proteinkinases B [23].

Functional recovery and regeneration

T. Sehm et al. studied potential targets of miR-196 for tail regeneration in axolotl [24]. The authors confirmed that this microRNA directly influences the Pax7 gene and suppresses the levels of the expressed protein. Thus, this microRNA affects cell division during regeneration and produces a small tail phenotype. This protein produced the phenotype through a feedback loop with BMP4 and Msx1 (Msh homeobox 1) proteins. These proteins are necessary to control cellular proliferation in the spinal cord. As soon as miR-125 was determined as an important factor for regeneration, J.F. Díaz Quiroz et al. analyzed the effect of increased level of miR-125b in rats after SCI [25]. They injected a synthetic variant of miR-125b into the lesion site in 7 days after injury and showed reduced level of Sema4D, development of the glial scars and positive effect on functional recovery (improved movement in some animals). Y.M. Yu et al. analyzed the role of miR-133b in functional recovery after SCI. They found that this microRNA is important for SC regeneration in danio rerio. Regeneration is associated with reduced level of RhoA protein (RAS homolog gene family, member A) of small GTPase (guanosine triphosphate) [26]. The regularities of activation of this protein after SCI and its role in apoptosis of CNS cells have been studied [33]. Both proteins originating from myelin and

tumor necrosis factor directly activate Rho. Inactivation of Rho C3-05 (RAS homolog gene family, member C3-05, antagonist of RhoA) after SCI blocks augmentation of p75NTR protein (p75 neurotrophin receptor) and inhibits apoptosis. Rho C3-05 inactivation prevents apoptosis and stimulates regeneration. MiR-133b causes this reduction through direct interaction with RNA mediator RhoA. This is an important conclusion, since it was shown that inactivation of this GTPase leads to restoration of coordination between anterior and posterior limbs in mice [34].

Functional role of lncRNA in spinal cord injury

Recently, new characteristics of differentially expressed lncRNAs have been discovered in SCI. In particular, lncRNA-mediated modulation of glial activation and neuronal apoptosis has become an area of intensive research.

Glial activation

Glia may be activated within 1 day (microglia activation) and persist for months or even years (astrogliosis) after SCI [35—37]. In the model of acute blunt SCI in rats, it was found that the level of MALAT1 protein (metastasis associated lung adenocarcinoma transcript 1) is significantly increased within the damaged area of SC [38]. MALAT1 activates miR-199b and contributes to release of proinflammatory cytokines. Inhibition of spinal MALAT1 led to decrease in expression of microglial marker Iba-1 and proinflammatory cytokines in the epicenter of contusion and improvement of motor function of posterior limb. However, the role of MALAT1 in microglial polarization has not been studied in this research. Other authors found that expression of ncRNA lncSCIR1 is continuously decreased in 1, 4 and 7 days after moderate blunt SCI [39]. The amount of lncSCIR1 inversely correlated with expression of bone morphogenetic protein 7 (Bmp7) and adrenomedullin (Adm). These proteins contribute to spinal cord astrogliosis [40, 41]. Inhibition of lncSCIR1 stimulated migration and proliferation of cultivated astrocytes [39]. However, most functional studies were performed in vitro. Nevertheless, these studies ensured preliminary evidence that lncRNA can participate in gliogenesis after SCI.

Neuronal apoptosis

Neuronal death is the most obvious consequence of spinal cord injury, especially in acute phase of lesion. Therefore, the molecules-modulators of neuronal apoptosis constantly attract the attention of researchers. XIST (X-inactive specific transcript) was identified as one of the active lncRNAs with the greatest multiplicity of changes in the number of molecules in the model of SC contusion in mice [42]. Inhibition of XIST had a significant neuroprotective effect through activation of (PI3K)/AKT protein in damaged SC. Inhibition of XIST was followed by increased expression of miR-494. Then, the last one inhibited PTEN deletion. Reducing PTEN activated PI3K/AKT pathway and protected neurons from apoptosis.

Possible therapeutic approaches

The role of microRNA in SCI needs further study. However, there are multiple data on microRNAs as a new class of therapeutic targets [43—45]. MicroRNAs reduce protein levels in central nervous system through posttranscriptional regulation [16, 46]. Thus, inhibition of microRNA associated with a specific disease can eliminate the blockade of expression of the desired protein. On the contrary, introduction of microRNA mimetics can stimulate endogenous microRNA suppressing the desired gene [47]. Some modified RNAs may be used as pre-microRNA or as oligonucleotides against microRNA [48]. Oligonucleotides against microRNA are complementary nucleotides with reverse chain. Their stability and specificity are improved by chemical modifications. It was shown that oligonucleotides with 2'-O-methyl-modification are effective inhibitors of several cell lines and cultured neurons [49—51]. MicroRNAs mimic small, usually double-chained, chemically modified oligonucleotides which can be used to inhibit specific target proteins. The double-chained structure is necessary for effective association with RISC (RNA-induced silencing complex). One of the chains is a mature microRNA, and the complementary chain forms a complex with a sequence of mature microRNA [51]. There is still no evidence of efficacy of these simulators although they are often used in crop studies [52]. There are still many challenges to usy microRNAs as therapeutic targets including difficult introduction, possible effects on other genetic systems and ensuring safety. However, the strategy of manipulating microRNA in vivo for regulation of abnormal processes is becoming possible as a therapeutic approach. A better understanding of their biosynthesis and function will undoubtedly facilitate the development of microRNA therapy.

Conclusion

Spinal cord injury is a cause of disability in working-age population. This serious clinical problem is still requiring intensive research. Non-coding RNAs are also analyzed in this pathology. As a result, their importance in control of inflammation, acidosis, apoptosis, proliferation and regeneration was emphasized. Further studies of non-coding RNAs in spinal cord injury, identification of target genes and signal transmission pathways are needed. Non-coding RNAs participate in various cellular and tissue changes at all stages of spinal cord injury through interaction with a network of coding genes. Thus, deregulation of non-coding RNAs is a new approach to influence on molecular mechanisms in spinal cord inju-

ry. The ultimate aim is to develop an effective and safe therapeutic and diagnostic strategies for patients with spinal cord injury.

Authors' participation:
Concept and design of the study — O.B., N.K.
Collection and analysis of data — Sh.A., A.A., A.B.
Analysis of data — Sh.A., A.A., A.B.
Writing the text — I.G.
Editing — O.B., N.K.

The authors declare no conflicts of interest.

REFERENCES

1. Silva NA, Sousa N, Reis RL, Salgado AJ. From basics to clinical: A comprehensive review on spinal cord injury. Progress in Neurobiology. 2014;114:25-57. https://doi.org/10.1016/j.pneurobio.2013
2. Kumar R, Lim J, Mekary RA, Rattani A, Dewan MC, Sharif SY, Osorio-Fonseca E, Park KB. Traumatic Spinal Injury: Global Epidemiology and Worldwide Volume. World Neurosurgery. 2018;113:345-363. https://doi.org/10.1016/j.wneu.2018.02.033
3. Di Giovanni S, Knoblach SM, Brandoli C, Aden SA, Hoffman EP, Faden AI. Gene profiling in spinal cord injury shows role of cell cycle in neuronal death. Annals of Neurology. 2003;53(4):454-468. https://doi.org/10.1002/ana.10472
4. Nesic O, Svrakic NM, Xu GY, McAdoo D, Westlund KN, Hulsebosch CE, Zeiming Ye, Galante A, Soteropoulos P, Tolias P, Young W, Hart RP, Perez Polo JR. DNA microarray analysis of the contused spinal cord: Effect of NMDA receptor inhibition. Journal of Neuroscience Research. 2002;68(4):406-423. https://doi.org/10.1002/jnr.10171
5. Silver J, Miller JH. Regeneration beyond the glial scar. Nature Reviews Neuroscience. 2004;5(2):146-156. https://doi.org/10.1038/nrn1326
6. Sofroniew MV. Reactive astrocytes in neural repair and protection. Neuroscientist. 2005;11(5):400-407. https://doi.org/10.1177/1073858405278321
7. Herrmann JE, Imura T, Song B, Qi J, Ao Y, Nguyen TK, Korsak RA, Takeda K, Akira S, Sofroniew MV. STAT3 is a critical regulator of astrogliosis and scar formation after spinal cord injury. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2008;28(28):7231-7243. https://doi.org/10.1523/JNEUROSCI.1709-08.2008
8. Barnabé Heider F, Frisén J. Stem cells for spinal cord repair. Cell Stem Cell. 2008;3(1):16-24. https://doi.org/10.1016/j.stem.2008.06.011
9. Sahni V, Mukhopadhyay A, Tysseling V, Hebert A, Birch D, Mcguire TL, Stupp SI, Kessler JA. BMPR1 and BMPR1b signaling exert opposing effects on gliosis after spinal cord injury. Journal of Neuroscience. 2010;30(5):1839-1855. https://doi.org/10.1523/JNEUROSCI.4459-09.2010
10. Beattie MS, Farooqui AA, Bresnahan JC. Review of current evidence for apoptosis after spinal cord injury. Journal of Neurotrauma. 2000;17(10):915-925. https://doi.org/10.1089/neu.2000.17.915
11. Shuman SL, Bresnahan JC, Beattie MS. Apoptosis of microglia and oligodendrocytes after spinal cord contusion in rats. Journal of Neuroscience Research. 1997;50(5):798-808. https://doi.org/10.1002/(SICI)1097-4547(19971201)50:5<798::AID-JNR16>3.0.CO;2-Y
12. Chan CS, Elemento O, Tavazoie S. Revealing posttranscriptional regulatory elements through network-level conservation. PLoS Computational Biology. 2005;1(7):69. https://doi.org/10.1371/journal.pcbi.0010069
13. Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature. 2005;433(7027):769-773. https://doi.org/10.1038/nature03315
14. Hu JZ, Huang JH, Zeng L, Wang G, Cao M, Lu HB. Anti-apoptotic effect of microRNA-21 after contusion spinal cord injury in rats. Journal of Neurology. 2013;30(15):1349-1360. https://doi.org/10.1089/neu.2012.2748
15. Liu NK, Wang XF, Lu QB, Xu XM. Altered microRNA expression following traumatic spinal cord injury. Experimental Neurology. 2009;219(2):424-429. https://doi.org/10.1016/j.expneurol.2009.06.015
16. Kosik KS. The neuronal microRNA system. Nature Reviews Neuroscience. 2006;7(12):911-920. https://doi.org/10.1038/nrn2037
17. Bilen J, Liu N, Burnett BG, Pittman RN, Bonini NM. MicroRNA pathways modulate polyglutamine-induced neurodegeneration. Molecular Cell. 2006;24(1):157-163. https://doi.org/10.1016/j.molcel.2006.07.030
18. Schaefer A, O'Carroll D, Tan CL, Hillman D, Sugimori M, Llinas R, Greengard P. Cerebellar neurodegeneration in the absence of microRNAs. Journal of Experimental Medicine. 2007;204(7):1553-1558. https://doi.org/10.1084/jem.20070823
19. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, Lagarde J, Veeravalli L, Ruan X, Ruan Y, Lassmann T, Carninci P, Brown JB, Lipovich L, Gonzalez JM, Thomas M, Davis CA, Shiekhattar R, Gingeras TR, Hubbard TJ, Notredame C, Harrow J, Guigó R. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Research. 2012;22(9):1775-1789.
20. Ziu M, Fletcher L, Savage JG, Jimenez DF, Digicaylioglu M, Bartanusz V. Spatial and temporal expression levels of specific microRNAs in a spinal cord injury mouse model and their relationship to the duration of compression. Spine Journal. 2014;14(2):353-360.
21. Bhalala O, Pan L, Sahni V, McGuire TL, Gruner K, Tourtellotte WG, Kessler JA. microRNA-21 regulates astrocytic response following spinal cord injury. Journal of Neuroscience. 2012;32:17935-17947. https://doi.org/10.1523/JNEUROSCI.3860-12.2012
22. Izumi B, Nakasa T, Tanaka N, Nakanishi K, Kamei N, Yamamoto R, Nakamae T, Ohta R, Fujioka Y, Yamasaki K, Ochi M. MicroRNA-223 expression in neutrophils in the early phase of secondary damage after spinal cord injury. Neuroscience Letters. 2011;492(2):114-118. https://doi.org/10.1016/j.neulet.2011.01.068
23. Liu G, Keeler BE, Zhukareva V, Houlé JD. Cycling exercise affects the expression of apoptosis-associated microRNAs after spinal cord injury in rats. Experimental Neurology. 2010;226(1):200-206. https://doi.org/10.1016/j.expneurol.2010.08.032
24. Sehm T, Sachse C, Frenzel C, Echeverri K. MiR-196 is an essentials early-stage regulator of tail regeneration, upstream of key spinal cord Kettering events. Developmental Biology. 2009;334(2):468-480. https://doi.org/10.1016/j.ydbio.2009.08.008
25. Diaz Quiroz JF, Tsai E, Coyle M, Sehm T, Echeverri K. Precise control of miR-125b levels is required to create a regeneration-permissive environment after spinal cord injury: A cross-species comparison between salamander and rat. Disease Models and Mechanisms. 2014;7(6):601-611. https://doi.org/10.1242/dmm.014837
26. Yu YM, Gibbs KM, Davila J, Campbell N, Sung S, Todorova TI, Otsuka S, Sabaawy HE, Hart RP, Schachner M. MicroRNA miR-133b is essential for functional recovery after spinal cord injury in adult zebrafish. European Journal of Neuroscience. 2011;33(9):1587-1597. https://doi.org/10.1111/j.1460-9568.2011.07643.x
27. Houle JD, Morris K, Skinner RD, Garcia-Rill E, Peterson CA. Effects of fetal spinal cord tissue transplants and cycling exercise on the soleus muscle in spinalized rats. Muscle and Nerve. 1999;22(7):846-856.
28. Beaumont E, Houlé JD, Peterson CA, Gardiner PF. Passive exercise and fetal spinal cord transplant both help to restore motoneuronal properties after spinal cord transection in rats. Muscle and Nerve. 2004;29(2):234-242. https://doi.org/10.1002/mus.10539
29. Tillakaratne NJK, Mouria M, Ziv NB, Roy RR, Edgerton VR, Tobin AJ. Increased expression of glutamate decarboxylase (GAD67) in feline lumbar spinal cord after complete thoracic spinal cord transection. Journal of Neuroscience Research. 2000;60(2):219-230. https://doi.org/10.1002/(SICI)1097-4547(20000415)60:2<219::AID-JNR11>3.0.CO;2-F

30. Ying Z, Roy RR, Edgerton VR, Gómez-Pinilla F. Exercise restores levels of neurotrophins and synaptic plasticity following spinal cord injury. Experimental Neurology. 2005;193:411-419. https://doi.org/10.1016/j.expneurol.2005.01.015

31. Dupont-Versteegden EE, Houlé JD, Dennis RA, Zhang J, Knox M, Wagoner G, Peterson CA. Exercise-induced gene expression in soleus muscle is dependent on time after spinal cord injury in rats. Muscle and Nerve. 2004;29(1):73-81. https://doi.org/10.1002/mus.10511

32. Sayed D, He M, Hong C, Gao S, Rane S, Yang Z, Abdellatif M. MicroRNA-21 Is a downstream effector of AKT that mediates its antiapoptotic effects via suppression of fas ligand. The Journal of Biological Chemistry. 2010;285(26):20281-20290. https://doi.org/10.1074/jbc.M110.109207

33. Dubreuil CI, Winton MJ, McKerracher L. Rho activation patterns after spinal cord injury and the role of activated Rho in apoptosis in the central nervous system. Journal of Cell Biology. 2003;162(2):233-243. https://doi.org/10.1083/jcb.200301080

34. Dergham P, Ellezam B, Essagian C, Avedissian H, Lubell WD, McKerracher L. Rho signaling pathway targeted to promote spinal cord repair. Journal of Neuroscience. 2002;22:6570-6577. https://doi.org/10.1523/JNEUROSCI.22-15-06570.2002

35. Popovich PG, Wei P, Stokes BT. Cellular inflammatory response after spinal cord injury in Sprague Dawley and Lewis rats. The Journal of Comparative Neurology. 1997;377(3):443-464. https://doi.org/10.1002/(sici)1096-9861(19970120)377:3<443::aid-cne10>3.0.co;2-s

36. Watanabe T, Yamamoto T, Abe Y, Saito N, Kumagai T, Kayama H. Differential activation of microglia after experimental spinal cord injury. Journal of Neurotrauma. 1999;16(3):255-265. https://doi.org/10.1089/neu.1999.16.255

37. DePaul MA, Lin CY, Silver J, Lee YS. Combinatory repair strategy to promote axon regeneration and functional recovery after chronic spinal cord injury. Scientific Reports. 2017(1);7:9018. https://doi.org/10.1038/s41598-017-09432-6

38. Zhou HJ, Wang LQ, Wang DB, Yu JB, Zhu Y, Xu QS, Zheng XJ, Zhan RY. Long noncoding RNA MALAT1 contributes to inflammatory response of microglia following spinal cord injury via the modulation of a miR199b/IKKβ/NFκB signaling pathway. American Journal of Physiology. Cell Physiology. 2018;315(1):52-61. https://doi.org/10.1152/ajpcell.00278.2017

39. Wang J, Hu B, Cao F, Sun S, Zhang Y, Zhu Q. Down regulation of lncSCIR1 after spinal cord contusion injury in rat. Brain Research. 2015;22(1624):314-320. https://doi.org/10.1016/j.brainres.2015.07.052

40. Fuller ML, DeChant AK, Rothstein B, Caprariello A, Wang R, Hall AK, Miller RH. Bone morphogenetic proteins promote gliosis in demyelinating spinal cord lesions. Annals of Neurology. 2007;62(3):288-300. https://doi.org/10.1002/ana.21179

41. Zeng X, Lin MY, Wang D, Zhang Y, Hong Y. Involvement of adrenomedullin in spinal glial activation following chronic administration of morphine in rats. European Journal of Pain. 2014;18(9):1323-1332. https://doi.org/10.1002/j.1532-2149.2014.493.x

42. Gu S, Xie R, Liu X, Shou J, Gu W, Che X. Long coding RNA XIST contributes to neuronal apoptosis through the downregulation of AKT phosphorylation and is negatively regulated by miR494 in rat spinal cord injury. International Journal of Molecular Sciences. 2017;18(4):732. https://doi.org/10.3390/ijms18040732

43. Esau CC, Monia BP. Therapeutic potential for microRNAs. Advanced Drug Delivery Reviews. 2007;59(2-3):101-114. https://doi.org/10.1016/j.addr.2007.03.007

44. Mirnezami AHF, Pickard K, Zhang L, Primrose JN, Packham G. MicroRNAs: Key players in carcinogenesis and novel therapeutic targets. European Journal of Surgical Oncology. 2009;35(4):339-347. https://doi.org/10.1016/j.ejso.2008.06.006

45. Weiler J, Hunziker J, Hall J. Anti-miRNA oligonucleotides (AMOs): Ammunition to target miRNAs implicated in human disease? Gene Therapy. 2006;13(6):496-502. https://doi.org/10.1038/sj.gt.3302654

46. Krichevsky AM. MicroRNA profiling: From dark matter to white matter, or identifying new players in neurobiology. Scientific World Journal. 2007;7:155-166. https://doi.org/10.1100/tsw.2007.201

47. Liu NK, Xu XM. MicroRNA in central nervous system trauma and degenerative disorders. Physiological Genomics. 2011;43(10):571-580. https://doi.org/10.1152/physiolgenomics.00168.2010

48. Medina PP, Slack FJ. Inhibiting microRNA function in vivo. Nature Methods. 2009;6(1):37-38. https://doi.org/10.1038/nmeth0109-37

49. Meister G, Landthaler M, Dorsett Y, Tuschl T. Sequence-specific inhibition of microRNA- and siRNA-induced RNA silencing. RNA. 2004;10(3):544-550. https://doi.org/10.1261/rna.5235104

50. Poy MN, Eliasson L, Krutzfeldt J, Kuwajima S, Ma X, MacDonald PE, Pfeffer S, Tuschl T, Rajewsky N, Rorsman P, Stoffel M. A pancreatic islet-specific microRNA regulates insulin secretion. Nature. 2004;432(7014):226-230. https://doi.org/10.1038/nature03076

51. Schratt GM, Tuebing F, Nigh EA, Kane CG, Sabatini ME, Kiebler M, Greenberg ME. A brain-specific microRNA regulates dendritic spine development. Nature. 2006;439(7074):283-289. https://doi.org/10.1038/nature04367

52. Zhao X, He X, Han X, Yu Y, Ye F, Chen Y, Hoang T, Xu X, Mi QS, Xin M, Wang F, Appel B, Lu QR. MicroRNA-mediated control of oligodendrocyte differentiation. Neuron. 2010;65(5):612-626. https://doi.org/10.1016/j.neuron.2010.02.018

Received 01.11.2019
Accepted 28.02.2020