Research Progress of MicroRNA in Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) is a central nervous system disease with severe damage that causes partial or complete loss of movement and sensation below the injury segment, causing dysfunction. MicroRNAs (miRNAs) are a class of non-coding single-stranded RNA small molecules of approximately 18-25 nucleotides in length. Studies have shown that miRNAs play a regulatory role in the pathological process of spinal cord injury, which will provide a new target for the treatment of SCI. This article reviews the expression changes of microRNAs after spinal cord injury and the possible mechanisms of action in pathological processes.

Key Words: microRNA, spinal cord injury, regulation

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Introductio

Spinal cord injury (SCI) is a serious central nervous system injury disease characterized by disability and mortality. According to reports (Bhalala et al., 2013; Hu JZ et al., 2013a), there are more than 60,000 new cases of spinal cord injury in China each year, which has a huge impact on patients, families and society. Therefore, the treatment and prognosis of spinal cord injury have attracted a lot of attention. At present, the pathophysiological changes after spinal cord injury can be divided into two sections: primary injury and secondary injury according to the time of occurrence and the cause of formation. Secondary injury includes a series of pathophysiological changes such as inflammatory response, apoptosis, oxidative stress and glial scar formation caused by primary injury (Lu Yubao et al., 2018). Since primary injury largely determines the level of damage, research and treatment can be focused on mitigating and improving secondary damage from various cascades.

MicroRNAs (miRNAs) are a class of small RNAs encoded by endogenous genes that regulate the expression of target genes at both post-transcriptional or translational levels. Studies (He Qinqin et al., 2016) showed that in the rat SCI model, the expression of a large number of miRNAs was dysregulated at different time points, which was associated with the degree of injury and the type of injury, and miRNAs played a regulatory role in the pathological process. Therefore, to explore the role and molecular mechanism of miRNA in the pathogenesis of SCI, can provide a new idea and indicators for the clinical treatment and prognosis of SCI. In this paper, based on the research status and progress of miRNA expression changes in SCI and the mechanism of action, a comprehensive comparative analysis and feasible suggestions for this field are proposed.

The expression and regulation of miRNAs after spinal cord injury

The results show that the expression of miRNA in spinal cord tissue is much higher than other tissues, but the expression level of a large number of miRNAs after SCI is dysregulated, suggesting that miRNA may have a regulatory effect after SCI. However, there were significant differences in the number and level of miRNAs that were dysregulated in different experiments. It is currently believed that

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this difference is composed of multiple factors. First, the experimental animals used by the researchers have significant species differences, such as rats, humans, zebrafish, etc. So the experimental results have differences due to differences in species and individual differences. In addition, Strickland ER et al (Strickland et al., 2011) found that changes in the expression of miRNA-146 a and miR-129-2 were associated with variability in the severity of initial injury, which suggests that miRNA expression may be related to the severity of SCI. When miRNA act, it is partially or fully complementary to the 3'-untranslated region (3'-UTR) of the target gene for the purpose of inhibiting or degrading the target gene. In the prediction of miRNA target genes. When the target gene binds to the miRNA, only a few base complementary sequences are needed to complete the complementary pairing. Therefore, one miRNA may be used as a potential target gene locus for binding; similarly, the target gene can also be affected by many Regulation of miRNAs. At the same time, in the regulation of SCI, miRNA may also be a link in a pathway (Sun, 2015). Thus, this forms a complex network of miRNA regulation in spinal cord injury. At present, the relevant mechanisms of SCI secondary injury are complex, with the following contents accordingly:

(1) Inflammatory reaction: The expression level of inflammatory factors in the injured area is sharply increased, and the inflammatory reaction is further aggravated;

(2) Apoptosis: autonomous programmed death of nerve cells after SCI;

(3) Mitochondrial theory: SCI leads to partial mitochondrial dysfunction in cells;

(4) Mechanism of formation of glial scar and fibrotic scar: scar formation on the injured surface to build a blood-brain barrier and inhibit neuronal process regeneration.

Apoptosis after regulating spinal cord injury by miRNA

Apoptosis refers to the process of autonomously ordered death of damaged nerve cells undergoing partial gene regulation during secondary injury following spinal cord injury. During this process, many miRNAs promote or inhibit apoptosis through changes in expression levels, which may serve to suggest a role in limiting and improving secondary damage. miR-21 is a miRNA that is significantly upregulated after rat SCI expression. After the addition of antagomir-21 to the rat SCI model, it was found that miR-21 expression was decreased and apoptosis was promoted. This indicates that overexpression of miRNA-21 inhibits neuronal apoptosis after SCI, thereby further impairing damaged nervous system damage. In this experiment, programmed cell death gene 4 (PDCD4) was found to be a target gene for miRNA-21 (Hu JZ et al., 2013b). Zhang et al (Jiang et al., 2017) found that neuronal apoptosis can be reduced by the miR-21/PDCD4/ caspase-3 pathway. In addition, miR-21 directly targets PTEN (Phosphatase and tensin homolog) and FasL to regulate apoptosis (Hu et al., 2013c; Liu et al., 2018). Tao et, al. (Tao and Shi, 2016) found that miR-195 down-regulated after SCI and negatively regulated HLF-1α (hypoxia-inducible factor 1-α) to protect apoptosis, while overexpression of miR-195 enhanced apoptosis, indicating miR- Pro-apoptotic effect of 195. In terms of signaling pathway, Li et, al. (Li G et al., 2018) found that overexpression of miR-103 up-regulates SOX2 and inhibits MAPK/ ERK and JAK/STAT pathways to inhibit apoptosis. Yu et, al. (Yu et al., 2019) found that up-regulation of miR-494 expression in rat SCI inhibited SIRT1 expression, regulated p35 signaling pathway, and promoted neuronal apoptosis. Therefore, inhibition of expression of miR-494 after SCI serves to protect cell death. After rat SCI, miR-219-5 p was detected to be highly expressed and directly negatively regulated (Table 1).

Anti-inflammatory effects of miRNA after spinal cord injuryThe inflammatory response is an important event after spinal cord injury. The inflammatory response directly affects apoptosis and recovery of the nervous system. Therefore, inhibition of inflammatory responses in damaged tissues is extremely important for the recovery of the nervous system. Numerous studies have shown that miRNAs regulate inflammatory responses by modulating related inflammatory factors following spinal cord injury. MiR-30-5p was found to be down-regulated after SCI, while Neurod l was highly elevated in SCI model mouse microglia (Fu et al., 2018). Overexpression of miR-30-5 p or silencing Neurod l inhibited TNF-α9 (tumor necrosis factor), expressed three pro-inflammatory factors, IL-1β (interleukin 1-β) and IL-10 (leukocyte-mediated It is 10), which plays an anti-inflammatory role. In addition, miR-30-5P overexpression also up-regulated SPNE1, TXNL1, G-PX1 up-regulated to participate in oxidative stress, scavenging oxygen free radicals, and protecting nerve

Table 1. Up-regulated microRNAs after SCI.

miRNA species	Target gene	Results after miRNA changes	Studying team
miRNA-152	Hud,Naa15	Inhibition of neuronal processes	(Chen Wei, 2014; Wu Jun, 2012)
miRNA-21	FasL, PTEN, PDCD4	Inhibition of apoptosis and astrocyte hypertrophy	(Hu JZ et al., 2013b; Jiang Y et al., 2017; Hu JZ et al., 2013c; Liu R, 2018; Hu J et al., 2016; Bhalala et al., 2012)
miRNA-21-5p	Smad7	Promotion of fibrotic scar formation	(Wang W et al., 2018)
miRNA-223	Bax, Bcl-2,GluR2	Promotion of apoptosis and inhibition of nervous system function recovery	(Liu D et al., 2015)
miRNA-17	PTEN	Promotion of glial scar formation	(Luan Y et al., 2017)
miRNA-20a	Mcl-1	Promotion of apoptosis	(Liu XJ et al., 2015)
miRNA-93	EphA4	Promotion of outward growth of neuronal processes	(Chen X et al., 2016)
miRNA-494	CDK6	Promotion of astrocyte proliferation and inhibition of synaptic remodeling	(Yu X et al., 2019)
miRNA-136-5p	IKKβ,A20	Promotion of inflammatory response	(Deng G et al., 2019; He J et al., 2017)
miRNA-146a	IRAK1, TRAF6	Inhibition of inflammatory response	(Wei J et al., 2016)
miRNA-214-3p	Bcl2l2	Promotion of apoptosis	(Fan Y and Wu Y, 2017)
miRNA-219-5p	LRH-1	Promotion of apoptosis	(Li J et al., 2018)
miRNA-133b	RhoA	Promotion of axon regeneration	(Yu YM et al., 2011)

tissue. MiRNA-146a was significantly up-regulated 3-7 days after SCI, which inhibited the expression of TRAF6 and ZRAKI and inhibited the secretion of pro-inflammatory factors. The researchers also believe that the up-regulation of miRNA-146 a may be caused by pro-inflammatory factors. Caused by (Wei et al., 2016). After spinal cord injury, miRNA-128 is down-regulated in mouse microglia, and overexpression of miRNA-128 reduces the concentration of TNF-α, IL-1β and IL-6 (Yang et al., 2019). Overexpression of miR-210 mediates JAK-STAT signaling pathway, reduces the expression of MCPI (human monocyte chemoattractant protein), and slows the inflammatory response (Dai J et al., 2018a). Other studies have shown that (Deng et al., 2018; He J et al., 2017), miRNA-136-5p up-regulated after SCI is an important regulator of inflammatory response. NF-κB is an important transcription factor that activates the nucleus and interacts with target genes to promote the release of inflammation-related factors in rats. The A20 protein can negatively regulate NF-κB. Overexpression miRNA-136-5 p can increase the expression of NF-κB and inhibit the secretion of A20. Therefore, the infiltration of inflammatory cells in the spinal cord of rats is increased after SCI. Therefore, in addition to the protective effect of silencing miRNA-136-5p on spinal cord injury, miR-223 is up-regulated after SCI and may positively regulate Rhob to affect the inflammatory response (Sun, 2015) (Table 2).

miRNA regulation of nerve and blood vessel repair and regeneration after SCI

In the treatment of spinal cord injury, how to restore the function of the damaged nervous system is an important factor that directly affects the prognosis and living standards of patients. The resilience of the central nervous system is very limited. Studies have shown that miRNA process may be one of the regulatory factors. miR-152 has been shown to have a role in regulating neurological recovery after SCI. Chen Yu (Chen Wei, 2014) found that miR-152 is elevated in different types of SCI and cell growth is inhibited. In contrast, after inhibition of miR-152 expression, cell neurite outgrowth did not differ from the control group. Through gene prediction and qPCR experiments, HuD is a target gene of miR-152, and HuD can regulate the stability of MAP2, TaDu protein and GAP-43 and other related axonal growth protein target miRNAs, further affecting cell growth. Wu Hao (Wu, 2012) found that upregulated miR-152 negatively regulates Naa15 (N-terminal acetyltransferase), which affects the growth of axons and dendrites. At the same time, miR-152 can regulate proteins related to the growth of axons by multiple pathways targeting E2F7, KIF-6, ElavI4 and the like. miR-21 has been shown to have anti-apoptotic effects in previous studies, while Hu et al (Hu J et al., 2016) found that miR-21 may regulate angiogenesis in damaged nerve tissue. In vitro, miR-

Table 2. Down-regulated microRNAs after SCI.

miRNA species	Target gene	Results after miRNA changes	Studying team
miRNA-124a	calpain1	Promotion of apoptosis	(Chen Jinguo, 2013)
miRNA-30-5p	Neurod 1	Promotion of inflammatory response	(He QQ et al., 2016)
miRNA-125b	JAK1, STAT1	Promotion of apoptosis and inflammatory response and inhibition of axonal outgrowth	(Dai J et al., 2018b)
miRNA-126	SPRED1, PIK3R2, VCAM1	Promotion of inflammatory response and slowing of blood vessel growth	(Hu J et al., 2015)
miRNA-127-3p	mitoNEET	Promotion of apoptosis,inhibition of neuroplasticity and intensification of motor function defects	(He QQ et al., 2016)
miRNA-137	MK2	Promotion of apoptosis and inflammatory response	(Gao L et al., 2018)
miRNA-195	HIF-1α	Inhibition of apoptosis	(Tao and Shi, 2016)
miRNA-210	-	Promotion of inflammatory response	(Dai J et al., 2018a)
miRNA-409	ZNF366	Slow recovery of nervous system function	(Lin CA et al., 2018)
miRNA-145	c-myc	Glial cells hyperplasia	(Wang CY et al., 2015)
miRNA-223-3p	RIP3	Promotion of apoptosis and inflammatory response	(Wang Y et al., 2019)

21, which is highly expressed after SCI, targets the expression of metalloproteinase inhibitor 3 (TIMP3). Promotes the secretion of two pro-angiogenic factors, matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9), which play an active role in blood vessel growth. Conversely, the application of antagomir-21 attenuated this angiogenesis. This suggests that overexpression of miR-21 promotes angiogenesis and contributes to the recovery of nerve tissue. Chen et al (Chen X et al., 2016) found that up-regulated miR-93 can inhibit the expression of EphA4, which is accompanied by a decrease in phosphorylation of Ephexin and inhibition of RhoA activity, which promotes the growth of neuronal neurites to some extent. DAI et al (Dai J et al., 2018b) found that miR-125b expression levels were down-regulated after SCI. Overexpression of miR-125b reduces the phosphorylation levels of JAKI and STATI, thereby inhibiting the recovery of nerve damage. Similarly, high expression of miR-223 after spinal cord injury also regulates the expression level of CD31 (platelet-endothelial cell adhesion molecule) to inhibit vascular recovery, while inhibition of high expression of miR-223 after SCI significantly increases CD31 expression to promote Vascular regeneration (Strickland et al., 2011).

Regulatory effect of miRNA on glial cells and scar formation after SCI

In the experiment, model animals generally showed glial cell proliferation, hypertrophy and scar formation in the damaged area after SCI. This plays a positive role in repairing the blood-brain barrier and preventing inflammatory reactions in the early stages of injury. Subsequent glial scars and fibrotic scars may hinder axonal regeneration to some extent and affect the recovery of nervous system function. Therefore, astrocytes may play a dual role in SCI (Hu JZ et al., 2013c). Studies have shown that miR-21 is expressed in the injured area higher than the uninjured area after SCI, and this overexpression inhibition is compared with inhibition of miR-21 expression. Atrophy of astrocytes (Bhalala et al., 2012). Liu et al (Liu et al., 2018) found that miR-21 is a key factor regulating astrocyte proliferation and glial scar and fibrotic scar formation after spinal cord injury. TGF-β1 (transforming growth factor-β) upregulates miR-21 by binding to TGF-β receptor and SMADs signaling, which directly targets PTEN to regulate the P13 K/ AKT/ mTOR pathway affecting cell viability. C-myc and GFAP have been shown to be target genes for miR-145. By overexpressing miR-145, the expression of these two target genes can be inhibited, thereby reducing the proliferation of astrocytes and reducing the formation of scars (Wang CY et al., 2015). Spinal neurotrophic factor (brain-derived nerve growth factor) promotes nerve regeneration and differentiation after SCI. Zhang et al. (Zhang K et al., 2017) miR-211 directly targets BDNF to inhibit its expression, thereby attenuating the proliferation of astrocytes. These findings may provide new targets for the chronic phase of SCI treatment.

Conclusion and Prospect

Since Li et al., miRNA-related research has developed rapidly, and a large number of research results have been obtained, including the regulation of miRNA after spinal cord injury, which involves the regulation of miRNAs on secondary damage following spinal cord injury such as inflammatory response, apoptosis and glial scar formation. However, most of these studies only studied for a single target and are relatively fragmented. Therefore, future research directions should focus on the upstream and downstream molecules of specific miRNAs and the involved signaling pathways, and the interaction of different miRNAs to construct a complete miRNA regulatory network.

Nowadays, the use of miRNA drugs to treat hepatitis C carries out in Phase II clinical trials (Hydbring and Badalian-Very, 2013), which has greatly encouraged the use of miRNA-related drugs for the treatment of spinal cord injury. In a large number of experiments, various miRNA mimetics, inhibitors, and agonists have been widely used; many traditional Chinese medicine extracts such as ligustrazine, anthraquinone polysaccharide (Fan and Wu, 2017) have also been shown to regulate miRNA action. Therefore, the research direction of miRNA in the field of spinal cord injury can also focus on the exploration and development of various microRNA-related drugs and the selection of drug delivery methods under SCI conditions, providing a reliable and effective solution for the clinical treatment of spinal cord injury.

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