非编码RNA在脊髓损伤中的作用

阳庆林[1] 王一坤[1] 秦庆庆[1] 兰志杰[1] 郭浩然[1] 王勇平[1,2]*

([1]兰州大学第一临床医学院, 兰州 730000; [2]兰州大学第一医院骨科, 兰州 730000)

摘要 脊髓损伤(spinal cord injury, SCI)是一种较为严重的中枢神经系统疾病, 具有较高的致残率和致死率, 其临床症状取决于病变的位置和严重程度。目前, 尚缺乏行之有效的治疗手段来治疗脊髓损伤。近来研究证实, 非编码RNA在脊髓损伤的发生发展过程中发挥重要的调节作用。该文主要就非编码RNA的分类及功能、非编码RNA在脊髓损伤致病过程中的作用机制进行综述, 重点研究非编码RNA在脊髓损伤后的炎症反应、线粒体功能障碍、氧化应激、兴奋性氨基酸毒性、血管生成、细胞自噬、细胞凋亡等过程中的作用机制, 试图明确脊髓损伤的分子机制, 寻找脊髓损伤特异性诊断标志物和关键治疗靶点。

关键词 脊髓损伤; 非编码RNA; 血管生成; 炎症反应; 氧化应激; 细胞自噬; 细胞凋亡

Role of Non-Coding RNA in Spinal Cord Injury

YANG Qinglin[1], WANG Yikun[1], QIN Qingqing[1], LAN Zhijie[1], GUO Haoran[1], WANG Yongping[1,2]*

([1]*The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China*; [2]*Department of Orthopedics, the First Hospital of Lanzhou University, Lanzhou 730000, China*)

Abstract SCI (spinal cord injury) is a serious disease of the central nervous system, with a high disability rate and fatality rate, and its clinical symptoms depend on the location and severity of the lesion. At present, there is no effective treatment for spinal cord injury. Recent studies have confirmed that non-coding RNAs play an important regulatory role in the occurrence and development of spinal cord injury. This paper mainly reviews the classification and function of non-coding RNAs and the mechanism of action of non-coding RNAs in the pathogenesis of spinal cord injury, focusing on the mechanism of action of non-coding RNAs in the inflammatory response, mitochondrial dysfunction, oxidative stress, excitatory amino acid toxicity, angiogenesis, autophagy, apoptosis and other processes after spinal cord injury. This paper attempts to clarify the molecular mechanism of spinal cord injury and search for specific diagnostic markers and key therapeutic targets of spinal cord injury.

Keywords spinal cord injury; non-coding RNA; angiogenesis; inflammatory reaction; oxidative stress; autophagy; apoptosis

脊髓损伤(spinal cord injury, SCI)是一种由外伤、血肿、感染以及肿瘤等多种因素导致的中枢神经系统病变, 发病率和残疾率较高, 其主要表现为损伤水平以下的感觉和运动功能部分或完全丧失[1-2]。原发性脊髓损伤通常是由直接创伤(如车辆事故、摔倒、暴力或运动期间的挫伤和压迫)和病理改变(如癌症)导致的急性脊髓受压和神经元细胞快速死亡[2-3]。继发性脊髓损伤是在原发性损伤的基础上发生的一系

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*通讯作者。Tel: 15095369802 , E-mail: wangyp312@163.com

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*Corresponding author. Tel: +86-15095369802, E-mail: wangyp312@163.com

列级联反应, 从而导致神经元死亡, 且继发性损伤比原发性损伤更加复杂[4-5]。脊髓损伤的病因和分子机制较为复杂, 且损伤的脊髓再生能力差[6-7]。目前, 脊髓损伤的治疗手段尚未取得令人满意的效果。因此, 为了找到一种新的治疗策略来促进脊髓损伤患者的功能恢复, 有必要进一步认识脊髓损伤的细胞和分子机制。近来研究表明, 非编码RNA(non-coding RNA, ncRNA)在脊髓损伤的致病过程中发挥重要作用, 或可为脊髓损伤的治疗带来新方向。本文就非编码RNA的分类及功能、非编码RNA在脊髓损伤致病过程中的作用机制进行综述, 以期为非编码RNA与脊髓损伤的相关研究提供参考及为脊髓损伤的诊疗提供新策略。

1 非编码RNA的分类和功能

人类基因组测序表明, 基因组主要由非蛋白质编码DNA组成, 只有大约3%的基因最终会编码蛋白质[8-9]。非编码RNA是指不能编码产生蛋白质的RNA分子, 参与了胚胎发育、细胞增殖、细胞分化、细胞凋亡、机体感染以及免疫应答等病理生理的调控, 与恶性肿瘤、心血管系统疾病、神经系统疾病和免疫性疾病等的发生发展有着密切关系[8,10-12]。非编码RNA的种类较多, 包含lncRNA、miRNA、piRNA、snoRNA、siRNA和环状RNA(circular RNA, circRNA)等。研究发现, lncRNA、miRNA和circRNA在脊髓损伤的病理过程中起着关键作用。

1.1 lncRNA

lncRNA是一类长度超过200个核苷酸且不编码蛋白质的RNA分子, 与细胞生长、细胞周期、细胞分化、细胞凋亡和炎症反应等生理病理过程密切相关[13]。值得注意, lncRNA在肿瘤疾病、心血管疾病、免疫性疾病和神经系统疾病等的恶性生物医学过程中发挥着重要作用[13-14]。随着测序技术的飞速发展, lncRNA对基因表达的转录调控机制不断被阐明。lncRNA可以通过与蛋白质、DNA和其他RNA等相互作用, 在转录水平或转录后水平等调控基因表达, 并参与染色质核内运输、原癌基因活化调节、免疫细胞分化和免疫系统调控等重要过程[11,13]。据报道, lncRNA显示出比mRNA更特异性的表达谱, 通常被认为具有精细的调节机制。

1.2 miRNA

miRNA是一种长度为18~24个核苷酸的RNA分子, 通过控制mRNA的稳定性和翻译来调控基因表达的转录后调控[15]。miRNA的基因通过RNA聚合酶II转录得到初级发夹转录物(pri-miRNA), 核糖核酸酶Drosha将pri-miRNA切割成大小约70 nt的茎环前体miRNA(pre-miRNA), 然后前体miRNA由细胞质核糖核酸酶Dicer进一步加工生成成熟的miRNA[15-16]。miRNA可以通过碱基互补配对的方式识别靶mRNA, 并根据互补程度的不同指导沉默复合体降解靶mRNA或者阻遏靶mRNA的翻译, 从而控制mRNA的稳定性和翻译来介导基因表达的转录后调控[17-18]。

1.3 circRNA

circRNA是一类较为特殊的非编码RNA分子, 由真核生物中外显子的前体mRNA反向剪接产生[19]。与传统的线性RNA相比, circRNA分子呈封闭环状结构, 不受RNA外切酶的影响, 表达稳定且不易被降解。circRNA通常以低水平表达, 并且通常表现出细胞类型特异性和组织特异性, 可以在表观遗传水平、转录和转录后水平参与调控基因表达[20]。circRNA具有隔离miRNA或蛋白质、调节转录及干扰剪接、翻译产生多肽等功能, 在生物体的生理病理过程中发挥至关重要的作用[19,21]。

2 脊髓损伤与非编码RNA

根据损伤时间和病理机制, 可以将脊髓损伤分为初始阶段的原发性损伤和随后的继发性损伤, 且继发性损伤比原发性损伤更加复杂。继发性脊髓损伤的病理过程分为急性期、亚急性期以及慢性期。急性期为损伤后的48 h, 主要病理表现为血管损伤引起出血, 进而导致组织水肿和缺血等[1-2]。血管缺血、血容量不足或低灌注会导致离子失衡、兴奋性氨基酸毒性、自由基过度产生和炎症反应, 最终导致细胞死亡和组织破坏[51]。脊髓损伤后, 细胞膜损伤会使电压门控的Ca^{2+}活化或钙泄露, 从而导致细胞内Ca^{2+}含量进一步升高; 细胞内Ca^{2+}水平的升高会促进谷氨酸的释放, 使谷氨酸水平在损伤部位积累到神经毒性水平; 同时细胞内Ca^{2+}浓度升高会破坏离子稳态并损害正常的线粒体功能, 从而导致自由基产生和脂质过氧化[44,52]。除此之外, T细胞、巨噬细胞、小胶质细胞和中性粒细胞也将迅速浸润神经元组织, 释放的白细胞介素-1β(interleukin-1β, IL-1β)、白细胞介素-1α(interleukin-1α, IL-1α)、肿瘤坏

死因子-α(tumor necrosis factor-α, TNF-α)和IL-6等细胞因子会使神经元发生退行性变[31,38]。如果继发性急性损伤持续存在, 则进入亚急性损伤阶段, 发生神经元凋亡、轴突脱髓鞘、Wallerian变性、轴突重塑和胶质瘢痕形成等病理变化; 如果继发性亚急性损伤持续存在, 则进入继发性慢性损伤阶段, 主要病理变化为形成囊腔、轴突枯死和胶质瘢痕[3,73]。研究表明, 在上述脊髓损伤的病理过程中, 相关非编码RNA呈现出差异性表达, 并通过不同的分子机制调控脊髓损伤。

2.1 相关非编码RNA调控血管生成

血管损伤是促进继发性损伤的重要机制。小血管和毛细血管的损伤会促进白细胞和红细胞的渗出, 对受伤的脊髓组织施加压力并进一步破坏血液供应, 加重局部血管紊乱, 进而导致血管痉挛; 血管缺血、血容量不足和低灌注的发生最终会导致细胞死亡和组织破坏[22-23]。因此, 对于治疗脊髓损伤而言, 如何促进血管生成并向受伤的脊髓提供氧气、生长因子和其他营养因子等是至关重要的。研究表明, 非编码RNA在脊髓损伤后的血管生成过程中起着重要作用[24]。X染色体三角形四肽重复蛋白(ubiquitously transcribed tetratricopeptide repeat on chromosome X, UTX)是一种组蛋白脱甲基酶, 在脊髓损伤后出血、血细胞浸润、炎症以及神经元和寡突细胞的细胞死亡中发挥重要作用[25]。研究发现, UTX的表达在脊髓损伤后显著上升, 而*UTX*的敲除可以通过调节miR-24的启动子超甲基化促进脊髓损伤后的血管再生[26]。外泌体是一种细胞外囊泡, 含有蛋白质、代谢物、液体和核酸等不同的成分; 外泌体干预是脊髓损伤治疗中的重要治疗策略之一[27-28]。脊髓损伤后, 来源巨噬细胞外泌体的miR-155通过抑制细胞因子信号转导6(suppressors of cytokine signalling 6, SOCS6)诱导的p65泛素化和降解来激活NF-κB通路, 从而损害血管内皮细胞的线粒体功能, 进而加剧血–脊髓屏障(blood-spinal cord barrier, BSCB)完整性的破坏[29]。此外, 过表达的miR-325-3p可以保护血管壁的完整性, 减少炎症的渗透, 并改善脊髓损伤后的运动功能[30]。

2.2 相关非编码RNA调控炎症反应

脊髓损伤后, T细胞、巨噬细胞、小胶质细胞和中性粒细胞等将迅速浸润神经元组织, 释放的IL-1β、IL-1α、TNF-α和IL-6等细胞因子会使神经元发生退行性变。同时, 脊髓实质内出血会提高促炎细胞因子的水平, 并将炎症细胞(巨噬细胞、中性粒细胞和淋巴细胞)募集到脊髓中, 进一步加重脊髓肿胀和损伤。研究表明, 过度表达miR-182减轻了脊髓组织的炎症反应, 并减少了TNF-α、IL-6和IL-1β的表达水平[31]; 进一步实验表明, miR-182通过阻断IKKβ/NF-κB通路来抑制炎症反应, 从而改善了炎症反应诱发的脊髓损伤[31]。另一项研究发现, 含有miRNA-22的间充质干细胞(mesenchymal stem cell, MSC)衍生细胞外囊泡(extracellular vehicle, EV)显著降低组织中的炎症因子水平和抑制小胶质细胞的激活, 从而缓解大鼠脊髓损伤后的炎症反应和促进神经功能恢复[32]。此外, miR-221通过靶向TNF-α抑制炎症反应和氧化应激, 从而促进脊髓损伤的功能恢复[33]。LncRNA主要通过与蛋白质、DNA和miRNA等的相互作用, 在转录水平或转录后水平等调控基因表达, 从而调节机体的病理生理过程。AN等[34]研究表明, lncRNA NEAT1的下调通过影响miR-211-5p/MAPK1轴来缓解脊髓损伤的炎症反应。此外, lncRNA GAS5通过影响miR-93/PTEN轴削弱脊髓损伤后的炎症反应, 并改善脊髓损伤的运动功能[35]。ZHOU等[36]研究表明, lncRNA MALAT1通过上调miR-199b来抑制NF-κB信号通路的激活, 从而抑制脊髓损伤后小胶质细胞的炎症反应。同样, lncRNA Airsci的下调通过抑制NF-κB信号通路减轻炎症反应, 从而减轻脊髓组织损伤, 并促进脊髓损伤大鼠运动功能的恢复[37]。环状RNA是一类保守的内源性非编码RNA。CHEN等[38]证明, 下调环状RNA Prkcsh通过上调miR-488的表达减少体外炎症细胞因子的分泌量, 从而抑制脊髓损伤后的炎症反应。

2.3 相关非编码RNA调控线粒体功能

线粒体是除哺乳动物红细胞外的所有细胞类型中的基本细胞器, 在诸多关键生物过程(如生物能量的产生、活性氧的生物合成、钙稳态的控制和细胞死亡的触发等[39])中起着重要作用。线粒体功能障碍在神经系统疾病中充当重要角色[40-41], 如线粒体功能障碍会导致活性氧(reactive oxygen species, ROS)的产生增加, 从而致使神经细胞死亡[42]。线粒体膜蛋白MitoNEET是miR-127调节轴突生长和脊柱神经元种群的直接靶标之一。研究表明, miR-127通过抑制MitoNEET的表达来影响线粒体功能, 从而

促进神经元细胞凋亡[43]。另一项研究表明, 来源于巨噬细胞外泌体的miR-155通过抑制SOCS6诱导的p65泛素化和降解激活NF-κB通路, 从而损害血管内皮细胞的线粒体功能, 加剧脊髓损伤[29]。尽管非编码RNA参与调节脊髓损伤后的线粒体功能障碍, 但非编码RNA调节脊髓损伤的大部分相关机制尚未被完全了解。因此, 需要进一步的实验来确认非编码RNA在线粒体中的作用机制。

2.4 相关非编码RNA调控氧化应激

氧化应激是指体内氧化与抗氧化作用失衡, 高水平ROS和活性氮(reactive nitrogen species, RNS)的产生会引起多种损伤。研究发现, miR-219-5p在脊髓损伤后表达明显下调, 同时炎症因子(TNF-α、IL-1β和IL-6)、ROS和神经源性分化蛋白2(neuronal differentiation factor 2, NEUROD2)的水平明显升高; 而miR-219-5p模拟物转染逆转了这种情况[44]。此外, miR-99a通过抑制烟酰胺腺嘌呤二核苷酸磷酸氧化酶4(nicotinamide adenine dinucleotide phosphooxidase 4, NOX4)的表达, 从而缓解LPS诱导的PC12细胞的炎症、凋亡和脊髓损伤后氧化应激的进展[45]。DING等[46]研究表明, miR-7a的上调通过抑制NF-κB通路来缓解脊髓损伤诱导的氧化应激, 并抑制细胞凋亡。研究发现, lncRNA GAS5通过与CUGBP Elav样家庭成员2(CUGBP Elav-like family member 2, CELF2)结合, 促进鸟嘌呤核苷酸转换因子1(Vav guanine nucleotide exchange factor 1, VAV1)的表达, 从而加剧脊髓损伤后的氧化应激和细胞损伤[47]; 另一项研究发现, lncRNA CASC9在脊髓损伤大鼠和LPS诱导的PC12细胞中表达明显下调, 而miR-383-5p表达上调, 同时丙二醛(MDA)、乳酸脱氢酶(LDH)、TNF-α和IL-1β水平显著升高; 而CASC9的过度表达抑制了miR-383-5p表达, 同时降低了MDA、LDH、TNF-α和IL-1β的表达水平[48]; 这表明lncRNA CASC9可以通过海绵miR-383-5p减轻乳酸脱氢酶介导的脊髓损伤氧化应激和炎症反应, 从而抑制脊髓损伤的进展。YAO等[49]在脊髓损伤大鼠中观察到circ_014260和血小板反应蛋白1(thrombospondin-1, THBS1)的表达水平增加以及miR-384的表达水平减少, 敲除circ_014260的表达可以抑制脊髓损伤大鼠的神经元凋亡和氧化应激。此外, 外泌体circZFHX3通过海绵miR-16-5p促进胰岛素样生长因子1(insulin-like growth factor-1, IGF-1)的表达, 从而抑制经LPS诱导的BV-2细胞的凋亡、炎症和氧化应激[50]。

2.5 相关非编码RNA调控兴奋性氨基酸毒性

谷氨酸是一种丰富的兴奋性神经递质, 遍布中枢神经系统。脊髓损伤发生后, 由于过度释放谷氨酸和摄取谷氨酸过程受损, 细胞外谷氨酸水平在损伤部位周围积累到神经毒性水平, 大量Ca^{2+}流入对脊髓产生直接和间接的损害[51-53]。miR-23b可以通过控制NADPH氧化酶4(NADPH oxidase 4, NOX4)的表达, 从而影响疼痛动物模型中炎症因子和ROS的表达水平[54]。研究发现, 与健康动物相比, γ-氨基丁酸(GABA)和谷氨酸脱羧酶(GAD)的表达水平在疼痛动物模型中有所下降[55]。IM等[56]研究表明, miR-23b通过抑制NOX4的表达, 从而抑制炎症因子(COX2、IL-1β和TNF-α)的表达, 同时显著促进GABA和GAD的表达。miRNA-155可以调节谷氨酸(Glu)和γ-氨基丁酸(GABA)的表达, 从而缓解脑缺血的进展[57]。研究发现, 抑制NOX2的表达会降低渗透巨噬细胞数目、ROS的产生量以及促炎基因的表达水平, 同时抑制小胶质和巨噬细胞中miR-155的表达[58]。尽管非编码RNA参与调节脊髓损伤后的兴奋性氨基酸毒性作用, 但非编码RNA如何调节兴奋性氨基酸来调控脊髓损伤进展的大部分相关机制尚未被完全了解。因此, 需要进一步的实验来确认, 非编码RNA如何调节兴奋性氨基酸来调控脊髓损伤的进展。

2.6 相关非编码RNA调控细胞自噬

细胞自噬是细胞组分降解与再利用的重要机制, 可以预防细胞损伤, 促进细胞在营养缺乏的情况下存活, 并对细胞毒性刺激作出反应[59]。细胞自噬包括生理条件下的基础型自噬和应激条件下的诱导型自噬。基础型自噬对维持细胞内稳态以及细胞产物的合成、降解和循环再利用具有重要作用; 但自噬过度可能导致代谢应激、降解细胞成分, 甚至引起细胞死亡等。研究表明, 自噬在细胞稳态、衰老、免疫、肿瘤发生及神经退行性疾病等多种生理病理过程中发挥重要作用[59-61]。ZHOU等[62]研究表明, miR-384-5p通过抑制*Beclin-1*基因的表达来抑制神经元自噬体的形成。此外, miR-421-3p的过度表达显著降低了mTOR自噬通路的活性, 并促进了细胞自噬, 减少了神经元细胞凋亡数量, 促进了脊髓损伤后的功能恢复[63]。LI等[64]研究发现, miR-30c通过负性调控*Beclin-1*基因的表达抑制自噬体的形成, 从而抑制脊髓损伤大鼠的康复。miR-372在脊髓损伤大

鼠中的表达量显著增加, 而Beclin-1的表达量显著减少; 抑制miR-372的表达可以通过上调Beclin-1来促进细胞自噬, 从而减少神经细胞凋亡和促进脊髓损伤的恢复[65]。WANG等[66]通过从国家生物技术信息中心基因表达综合数据库中挖掘数据, 识别脊髓损伤中关键差异表达的lncRNA, 结果发现3个lncRNA分别与自噬、细胞外通信和转录因子网络有关, 其中XR_350851在脊髓损伤后的细胞自噬中起着重要作用。REN等[67]研究表明, lncRNA TCTN2的过度表达抑制了miR-216b的表达, 从而上调Beclin-1蛋白的表达; 而上调Beclin-1蛋白显著促进了细胞自噬, 从而改善了神经元凋亡并缓解了脊髓损伤。此外, lncRNA SNHG1通过海绵miR-362-3p激活JAK2/STAT3通路, 从而调节经LPS处理的PC12细胞的细胞活力、凋亡和自噬[68]。

2.7 相关非编码RNA调控细胞凋亡

细胞凋亡是一种由基因控制的细胞自主有序性死亡, 对内环境的稳定、机体的防御和免疫反应、肿瘤的发生发展, 以及生物体的进化等起着重要的作用, 具有重要的生物学意义及复杂的分子生物学机制。研究表明, miR-182通过抑制NF-κB通路的激活来抑制细胞凋亡和炎症反应, 从而改善脊髓损伤[31]。同样, miR-7a通过抑制NF-κB通路的激活, 从而抑制细胞凋亡, 并促进脊髓损伤恢复[46]。另一项研究发现, miR-212-3p通过靶向PTEN激活AKT/mTOR通路, 从而抑制LPS诱导的神经细胞凋亡, 并改善脊髓损伤大鼠的功能[69]。CUI等[70]研究发现, 诱导大鼠脊髓损伤后, lncRNA LEF1-AS1的表达显著上调, 而miR-222-5p的表达明显下调; 抑制LEF1-AS1的表达显著增强了miR-222-5p的表达和细胞活力, 并显著抑制了细胞凋亡。CAO等[35]研究表明, lncRNA GAS5的下调通过影响miR-93/PTEN轴, 从而抑制细胞凋亡和发挥抗炎作用。同样, lncRNA KCNQ1OT1通过影响miR-589-5p/NPTN轴, 促进小胶质细胞的炎症反应和凋亡[71]。尽管相关非编码RNA通过促进或抑制细胞凋亡来调控脊髓损伤的进展, 但相关的分子机制仍需要大量的研究来验证。

2.8 相关非编码RNA调控其他病理

脊髓损伤进入亚急性损伤阶段后, 会发生神经元凋亡、轴突脱髓鞘、Wallerian变性、轴突重塑和胶质瘢痕形成等病理变化[72]。如果继发性亚急性损伤持续存在, 则会进入继发性慢性损伤阶段, 主要病理变化为形成囊腔、轴突枯死和胶质瘢痕成熟[72-73]。LUAN等[74]研究发现, miR-17通过靶向PTEN并刺激PI3K/Akt/mTOR通路来调节脊髓损伤的进展, 抑制miR-17的表达可以减少脊髓损伤导致的胶质疤痕的形成。研究发现, miR-106-3p的表达在脊髓损伤后大鼠的小胶质细胞中明显上调; 抑制miR-106-3p的表达显著抑制了促炎因子的表达, 同时显著减小了受伤脊髓中的星形胶质细胞疤痕面积[75]。WANG等[76]研究结果表明, 上调的miR-155-5p可以通过激活cAMP/PKA通路来促进神经元轴突生长, 从而修复脊髓损伤。总体而言, 非编码RNA通过调节轴突重塑和胶质瘢痕形成来影响脊髓损伤的进展, 然而相关的分子机制仍需要大量的研究来验证。

3 总结与展望

脊髓损伤的致病过程是一个涉及到神经、免疫和血管等系统中多个相关靶点和信号通路的复杂过程, 并伴随着许多细胞和分子机制(图1)。目前, 没有较为有效的治疗方法来控制脊髓损伤之后的继发性损伤。近来研究表明, 脊髓损伤发生后, 相关非编码RNA的表达发生了明显变化, 且在脊髓损伤的病理过程中发挥关键作用。总之, 相关非编码RNA有希望成为脊髓损伤特异性较高的诊断标志物和关键治疗靶点, 将为脊髓损伤的修复提供一个新策略。

此外, 有几个问题将是进一步研究的重点及热点。首先, 关于非编码RNA与脊髓损伤的大多数研究都是临床前动物研究, 需要进一步转换应用于人类, 从而达到向临床过渡的目的。其次, 非编码RNA在脊髓损伤后的表达有上调, 也有下调, 对脊髓损伤产生保护性、有害性和其他影响。可以科学地调控相关非编码RNA的表达来促进轴突生长、细胞再生、神经重塑以及抑制脊髓损伤的病理过程, 从而促进脊髓损伤的功能恢复。此外, 非编码RNA的种类和数目较多, 调控关系网络复杂, 脊髓损伤中非编码RNA的大多数分子机制仍不清楚。因此, 需要更深入地研究和明确脊髓损伤中非编码RNA失调的原因和后果, 并选择最有前途的非编码RNA, 推动相关非编码RNA在脊髓损伤治疗中的应用。

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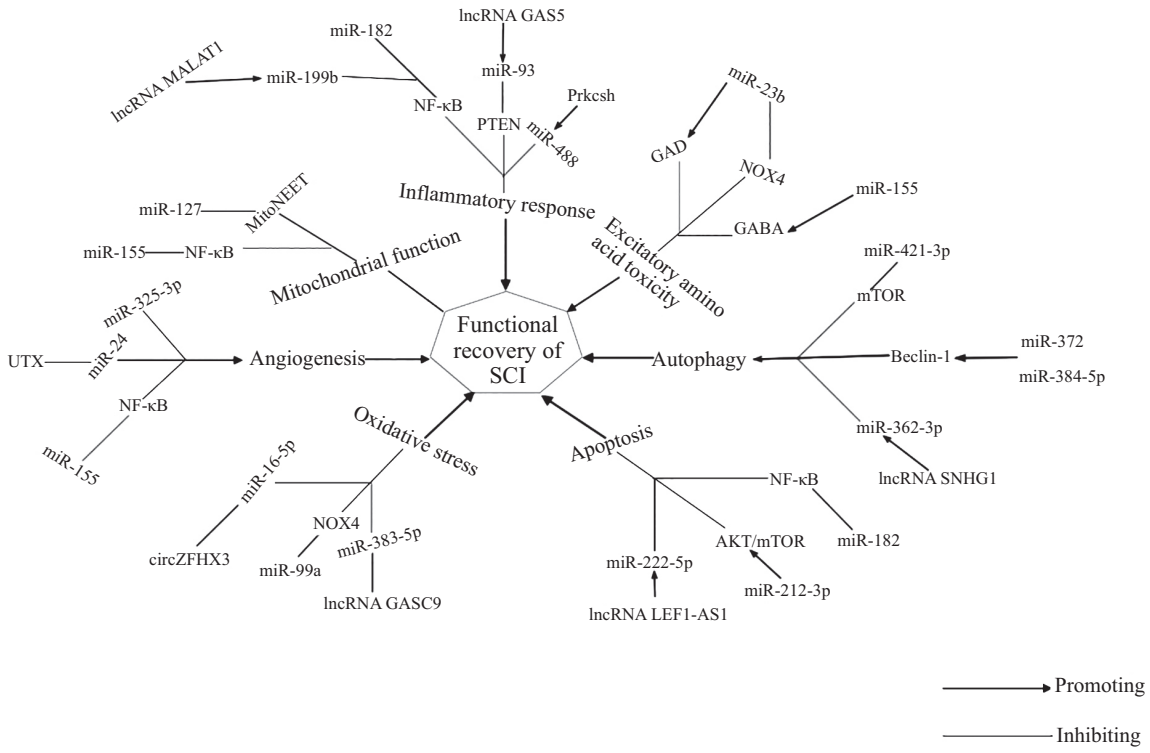

图1 非编码RNA调控脊髓损伤的机制示意图

Fig.1 Schematic diagram of the mechanism of non-coding RNA regulating SCI

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