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·综 述·

长链非编码RNA调控椎间盘退变的研究进展

何志伟[1],郭佳霖[1],李志军[2],杨学军[3] (1.内蒙古医科大学研究生学院,内蒙古 呼和浩特 010030;2.内蒙古医科大学基础医学院,内蒙古 呼和浩特 010110;3.内蒙古医科大学附属人民医院骨科,内蒙古 呼和浩特 010020)

[摘 要] 椎间盘退变(IDD)是导致腰痛的主要原因,目前在细胞和分子水平寻找IDD的机制得到了较多关注。已有研究报道长链非编码RNA(lncRNA)影响IDD的病理过程。本文综述了lncRNA对髓核细胞增殖、凋亡、衰老、自噬等方面的调控,总结了调控椎间盘内细胞增殖、凋亡和ECM合成与降解的lncRNA及相关靶基因或通路。值得注意的是,有的lncRNA不充当竞争内源性RNA(ceRNA),而是直接结合稳定相关微小RNA(miRNA),增强其miRNA表达从而调控IDD。此外,目前的研究主要报道的是lncRNA对椎间盘内髓核的调控,未来可进一步探究lncRNA对软骨终板和纤维环的调控,为lncRNA调控IDD提供更多的理论支持和依据。

[关键词] lncRNA;椎间盘退变;增殖;氧化应激;凋亡;衰老;细胞外基质

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Research progress of long non-coding RNAs in the regulation of intervertebral disc degeneration

HE Zhi-wei[1], GUO Jia-lin[1], LI Zhi-jun[2], YANG Xue-jun[3] (1.Graduate School, Inner Mongolia Medical University, Hohhot Inner Mongolia 010030, China; 2.School of Basic Medicine, Inner Mongolia Medical University, Hohhot Inner Mongolia 010110, China; 3. Department of Orthopedics, Affiliated People's Hospital of Inner Mongolia Medical University, Hohhot Inner Mongolia 010020, China)

Abstract: Intervertebral disc degeneration (IDD) is the main cause of low back pain. At present, more attention has been paid to finding the mechanism of IDD at the cellular and molecular levels. It has been reported that long non-coding RNAs (lncRNAs) affects the pathological process of IDD. This article reviews the regulation of lncRNAs on the proliferation, apoptosis, senescence and autophagy and other aspects of nucleus pulposus cells, and summarizes the lncRNAs and related target genes or pathways that regulate the proliferation, apoptosis, ECM synthesis and degradation of cells in the intervertebral disc. It is worth noting that some lncRNAs do not act as competing endogenous RNAs

[通信作者] 杨学军,E-mail:yangxuejun2004@126.com

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(ceRNAs),but directly bind to stable related microRNAs(miRNAs) and enhance their miRNAs expression to regulate IDD. In addition,current studies mainly report the regulation of lncRNAs on nucleus pulposus in the intervertebral disc. In the future, further exploration of the regulation of lncRNAs on the cartilage endplate and annulus fibrosus can provide more theoretical support and basis for lncRNAs regulating IDD.

Keywords: lncRNA; intervertebral disc degeneration; proliferation; oxidative stress; apoptosis; senescence; extracellular matrix

椎间盘退变(intervertebral disc degeneration,IDD)是导致腰痛的主要原因[1],遗传、环境、肥胖、性别和年龄均与IDD的发生有一定关系[2-3],但其分子生物学机制目前尚不清楚。长链非编码RNA(long non-coding RNA,lncRNA)是一组长度超过200个核苷酸的内源性非编码转录本[4],在对小鼠的全长cDNA文库进行大规模测序时被首次描述[5]。起初lncRNA被认为是“转录噪音”,而后发现其虽不编码蛋白质,但在生理和病理过程中仍发挥重要作用,包括基因组印记、基因表达调控、细胞分化和核质转运等[6-7]。同时lncRNA可作为竞争内源性RNA(competing endogenous RNA,ceRNA),通过其微小RNA(micro-RNA,miRNA)的响应元件与miRNA结合,从而调节miRNA的目标mRNA表达[8]。目前的研究显示,lncRNA在人类退变椎间盘组织中差异表达,并参与IDD的病理过程,包括炎症反应、细胞增殖与凋亡、细胞外基质(extracellular matrix,ECM)降解和氧化应激等多个过程[1,9-10]。因此,研究lncRNA在IDD过程中的精确调控机制,明确其调控椎间盘内细胞的靶基因和相关通路,可为早期预防或治疗IDD提供新的思路,有助于开发新的IDD诊治策略。

1 lncRNA调控椎间盘内细胞增殖

在IDD过程中椎间盘组织细胞增殖增加,可能是椎间盘组织对环境刺激的合成代谢反应导致[11]。同时,退变的椎间盘内可见细胞簇的形成,这可能是由髓核细胞的异常增殖所致。过度的细胞增殖可能会导致组织营养加速消耗或代谢废物的积累[11]。因此,明确在IDD过程中lncRNA调控髓核细胞增殖的相关靶基因或通路,并通过lncRNA来调控这些靶基因或通路,从而调节髓核细胞增殖,可为延缓IDD发挥重要作用。

有研究报道,lncRNA可通过调控Ki-67、增殖细胞核抗原(proliferating cell nuclear antigen,PCNA)和cyclin D1的表达来调控椎间盘内髓核细胞增殖。Wang等[12]发现过表达lncRNA RMRP可靶向miR-206促进Ki-67、PCNA和cyclin D1的表达进而促进细胞增殖。Tan等[13]报道,lncRNA SNHG1作为ceRNA,可抑制miR-326表达,促进PCNA和cyclin D1的表达。Chen等[14]报道,HOTAIR可作为ceRNA,抑制miR-130b对PTEN的调控,通过增强PTEN表达抑制AKT信号通路来降低cyclin D1蛋白表达,进而抑制NP细胞增殖。

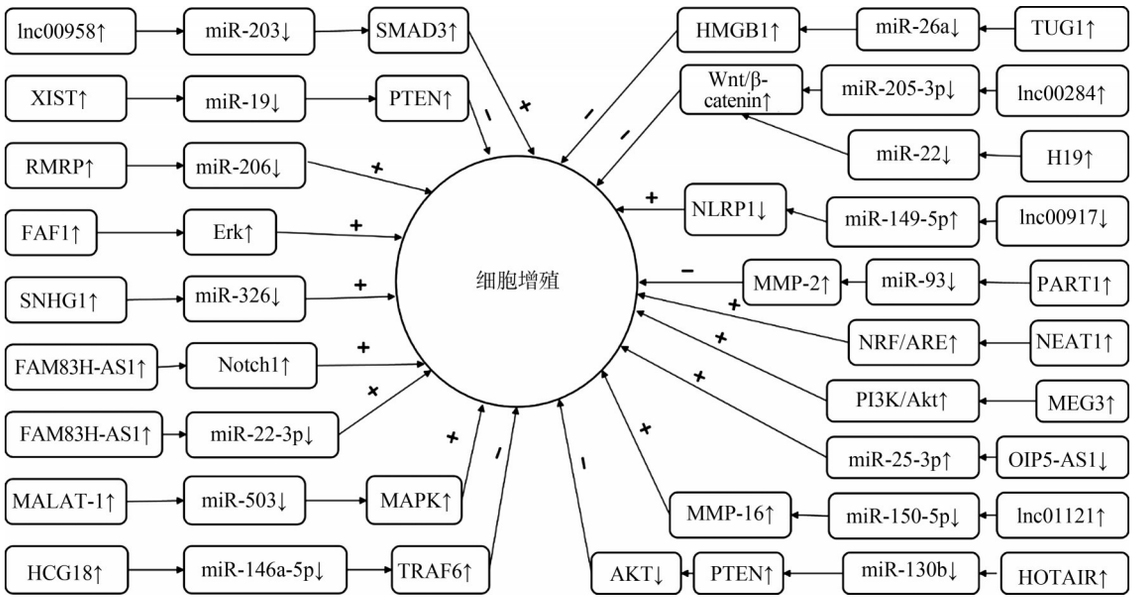
lncRNA还可通过信号通路来调控椎间盘内细胞增殖。Mi等[15]报道lncRNA FAF1在IDD患者髓核组织中表达上调。过表达FAF1可显著促进髓核细胞增殖,增加S期细胞的比例,其可能通过激活ERK通路来促进髓核细胞增殖。Tang等[16]发现TUG1是miR-26a的结合位点,TUG1通过靶向miR-26a/HMGB1轴抑制髓核细胞增殖,促进髓核细胞凋亡和ECM降解,且可能涉及NF-κB信号通路的激活。Zhu等[17]报道lnc00284可作为ceRNA抑制miR-205-3p表达,激活下游Wnt/β-catenin信号通路,抑制NP细胞增殖并促进ECM降解。Li等[18]发现lnc00917在退变的椎间盘组织和叔丁基过氧化氢(tert-butyl bydroperoxide,TBHP)处理的髓核细胞中表达上调,敲低lnc00917可促进髓核细胞增殖,其可通过靶向miR-149-5p/NLRP1轴对髓核细胞进行调控。本文总结了参与调控椎间盘内细胞增殖的lncRNA及相关靶基因或通路,见图1。

2 lncRNA调控椎间盘内氧化应激

氧化应激是由活性氧的产生和抗氧化系统的清除能力之间不平衡所致[10]。当IDD发生时,椎间盘内微环境改变,机械负荷和炎症因子等外源刺激会增加椎间盘细胞中活性氧的产生,同时椎间盘内抗氧化系统清除活性氧能力不足[19]。氧化应激产生高水平的活性氧可致核酸、脂质和蛋白质损伤,导致细胞毒性[19]。同时活性氧的过量产生可通过线粒体凋亡途径诱导髓核细胞凋亡,进一步加剧IDD[20]。Kang等[10]报道在TBHP诱导的人髓核细胞中过表达lncRNA ANPODRT可降低活性氧和丙二醛表达水平,抑制细胞色素C(cytochrome C,CytC)和活化的Caspase-3蛋白表达,该研究发现lncRNA ANPODRT通过激活Keap1-Nrf2信号传导保护髓核细胞免受氧化应激,减少细胞凋亡。

3 lncRNA调控椎间盘内细胞凋亡

细胞凋亡是一种程序性细胞死亡,主要表现为染色体浓缩、细胞体积减小、DNA降解和凋亡小体形成[21]。线粒体途径诱导细胞凋亡在IDD过程起重要作用[22-23]。Ding等[23]报道细胞的应激反应或凋亡信号可



↑:上调;↓:下调;+:促进细胞增殖;−:抑制细胞增殖

图1 参与调控椎间盘内细胞增殖的lncRNA及相关靶基因或通路

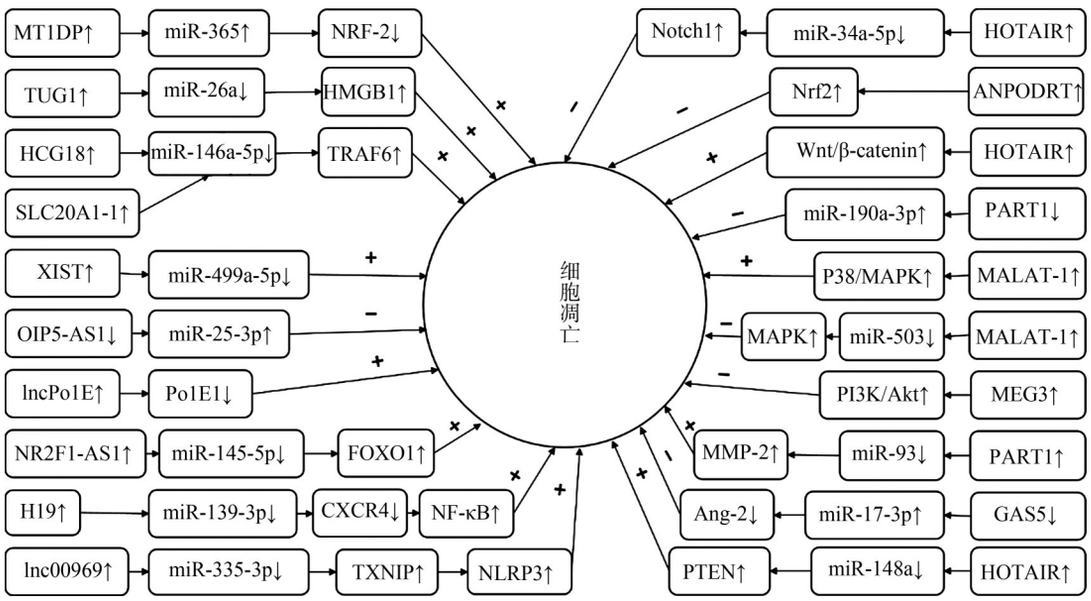
引起CytC从线粒体释放,然后与凋亡蛋白酶激活因子1(apoptotic protease activating factor-1,Apaf-1)、procaspase-9、ATP形成凋亡小体诱导Caspase-3的激活,触发半胱天冬酶级联反应,最终导致细胞凋亡。Bcl-2可作为抑制凋亡基因,阻止CytC从线粒体释放到细胞质,抑制细胞凋亡[23]。而Bax作为促凋亡基因,在接受凋亡信号后,会重新定位到线粒体表面,增加线粒体膜的通透性,促进CytC等线粒体相关促凋亡因子的释放,加剧细胞凋亡[24]。

有研究报道lncRNA GAS5可调控髓核细胞凋亡,Wang等[22]在髓核细胞中过表达GAS5后,发现其可通过下调Bcl-2和上调Caspase-3来促进细胞凋亡。Yu等[25]发现沉默GAS5可通过依赖miR-17-3p抑制血管生成素2的表达来降低髓核细胞凋亡和ECM降解。Xi等[1]发现,过表达lncRNA HCG18可抑制髓核细胞增殖,同时显著降低S期细胞比例并诱导细胞凋亡,还可增加巨噬细胞的迁移数量,抑制髓核细胞的成骨分化。HCG18可作为ceRNA下调髓核细胞中miR-146a-5p的表达,进而上调TRAF6表达以抑制髓核细胞生长并促进凋亡。Chen等[26]发现lncRNA SLC20A1-1也可作为ceRNA,通过miR-146a-5p/TRAF6轴促进肿瘤坏死因子-α(tumor necrosis factor -α,TNF-α)诱导的髓核细胞凋亡及巨噬细胞侵袭、迁移。与ceRNA机制不同,lncRNA MT1DP可直接结合稳定miR-365从而提高miR-365水平[27]。Liao等[28]报道MT1DP和miR-365在退变椎间盘髓核中显著上调,过表达MT1DP和miR-365可抑制髓核细胞活性,通过下调Bcl-2和上调Caspase-3诱导细胞凋亡,同时破坏线粒体膜降低线粒体功能,降低细胞清除活性氧的能力,进一步增加细胞凋亡,其机制可能与抑制NRF-2通路有关。

Li等[29]发现lncPolE在IDD患者髓核细胞中表达上调,其过表达可激活Caspase-3、Caspase-9和PARP诱导细胞凋亡;该研究亦发现,细胞内铁离子水平可能调节lncPolE水平,但其详细机制还需进一步研究。Shao等[30]发现HOTAIR在IDD患者髓核细胞中表达水平降低,HOTAIR可充当ceRNA,与miR-34a-5p结合,阻止miR-34a-5p对Notch1的降解,从而增强Notch信号来减少细胞凋亡。

MALAT1被报道参与调节IDD过程中的细胞凋亡[31-32]。Zheng等[31]报道MALAT1在IDD患者髓核细胞中表达下调,其可充当miR-503的ceRNA,并通过MAPK信号通路促进细胞增殖、抑制细胞凋亡和ECM降解。Jiang等[32]报道高浓度葡萄糖可促进大鼠软骨终板(cartilage endplate,CEP)细胞中MALAT1的表达,MALAT1通过p38/MAPK信号通路促进高糖诱导的大鼠CEP细胞凋亡。程宁等[33]报道MEG3在白细胞介素-1β(interleukin-1β,IL-1β)诱导的大鼠退变椎间盘髓核细胞中表达降低,MEG3过表达可能通过激活PI3K/Akt信号通路促进髓核细胞增殖,并抑制其凋亡。Yu等[34]报道lnc00969可作为ceRNA,抑制miR-335-3p对其靶基因TXNIP的调控,促进TXNIP激活NLRP3,进而促进髓核细胞凋亡。了解lncRNA对椎间盘内促凋亡基

因、抑制凋亡基因及相关通路的影响，并加以调控，有利于延缓IDD。有关参与调控椎间盘内细胞凋亡的lncRNA及相关靶基因或通路，见图2。



↑：上调；↓：下调；+：促进细胞凋亡；−：抑制细胞凋亡

图2 参与调控椎间盘内细胞凋亡的lncRNA及相关靶基因或通路

4 lncRNA调控椎间盘内细胞衰老

细胞衰老是细胞响应各种外部刺激而发生的不可逆的细胞周期停滞[35]。与非退变髓核细胞相比，退变髓核细胞表现出较慢的增殖和过多的细胞衰老[36]。Liang等[37]发现lnc-HRK-2:1过表达后，SA-β-gal染色结果显示髓核细胞中的衰老细胞数量显著增加，表明lnc-HRK-2:1的过表达可诱导髓核细胞衰老，其机制可能与CCL5和PNPT1的表达增加有关。Wang等[38]发现敲低H19可抑制髓核细胞衰老，减少H_2O_2诱导的髓核细胞中SA-β-gal阳性细胞数量，同时H19可作为ceRNA与LEF1竞争miR-22，促进Wnt/β-catenin信号转导，促进H_2O_2诱导的髓核细胞衰老、ECM降解并抑制细胞增殖。

5 lncRNA调控椎间盘内ECM合成与降解

椎间盘内的ECM成分主要包括胶原蛋白（Ⅰ型胶原蛋白和Ⅱ型胶原蛋白占大部分）、蛋白多糖（主要是聚蛋白多糖和少量的非胶原蛋白[39]。正常椎间盘内ECM的合成与分解处于动态平衡，当平衡被各种刺激打破，分解快于合成，就会引起IDD[40-41]。同时基质金属蛋白酶（matrix metalloproteinase,MMP）和含血小板结合蛋白基序的解聚素金属蛋白酶（a disintegrin and metalloprotease with thrombospondin motifs，ADAMTS）是降解胶原蛋白和聚蛋白多糖的主要酶，二者的许多成员参与ECM降解并且和IDD进展密切相关[41]。因此，对于lncRNA调控ECM合成，主要是其对Ⅱ型胶原蛋白和聚蛋白多糖表达的影响；对于lncRNA调控ECM降解，主要是其对MMPs和ADAMTSs成员表达的影响。

lncRNA NEAT1、XIST、SLC20A1、HOXC13-AS、GAS5、HOTAIR和lnc00958均可抑制Ⅱ型胶原蛋白和聚蛋白多糖的表达，同时促进MMPs和ADAMTSs的表达[42-48]。lncRNA NEAT1过表达可促进ADAMTS-4[42]、MMP-3和MMP-13[49] mRNA和蛋白表达，NEAT1可能通过激活ERK/MAPK信号通路[42]，也可通过调节NRF/ARE信号通路促进髓核细胞的ECM降解[49]。He等[43]报道在髓核细胞中过表达XIST也可促进MMP-3、MMP-13 mRNA和蛋白表达，其可通过靶向miR-499a-5p促进髓核细胞凋亡和ECM降解。此外，XIST可作为ceRNA结合miR-19[50]，GAS5作为ceRNA结合miR-26a-5p[46]，二者均可上调PTEN，并通过抑制PI3K/Akt通路来促进髓核细胞ECM降解。Yang等[44]报道过表达SLC20A1可使ADAMTS-4的mRNA和蛋白表达水平升高，SLC20A1充当ceRNA负调节miR-31-5p，促进miR-31-5p下游靶标MMP-3表达。Jing等[45]报道HOXC13-AS可作为ceRNA，竞争结合miR-4975p，以促进ADAMTS-5表达，从而促进MMP-3

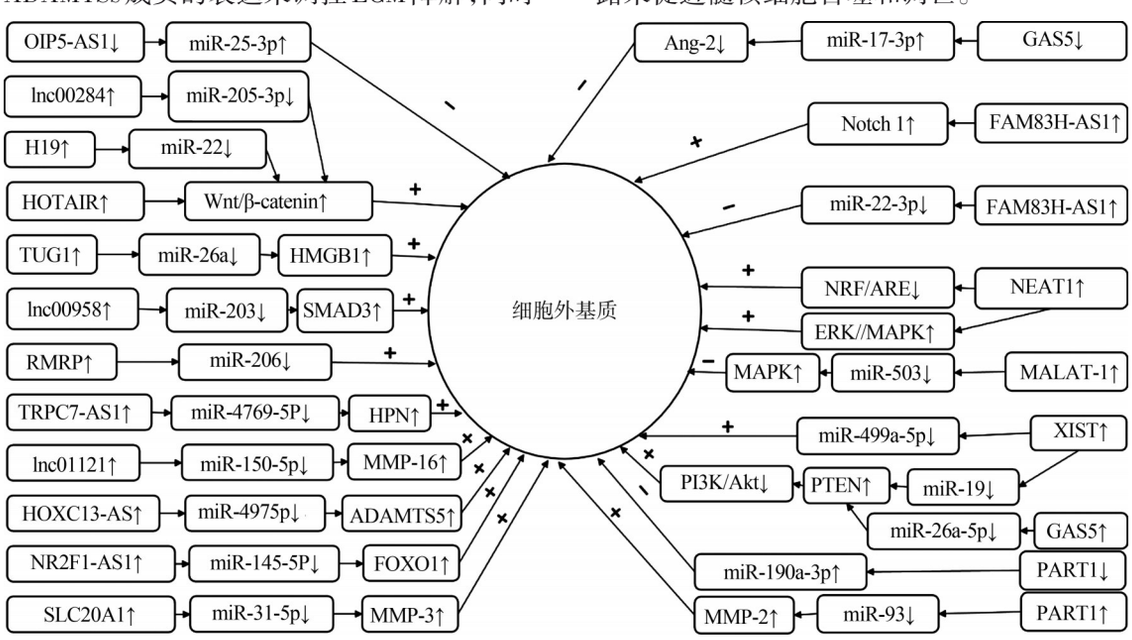
和ADAMTS-4表达。Zhan等[47]在髓核细胞中过表达HOTAIR,RT-qPCR显示MMP-3、MMP-9和MMP-10表达均上调,其对髓核细胞的影响是通过激活Wnt/β-catenin通路实现的。Zhao等[48]报道了lnc00958过表达促进MMP-2和MMP-13 mRNA表达,并通过调控miR-203/SMAD3促进髓核细胞增殖和ECM降解。

关于lncRNA PART1对ECM的调控,Gao等[51]报道PART1在IDD患者髓核细胞中表达升高,其通过miR-93/MMP-2通路促进IDD。Zhang等[52]报道敲低PART1可增强髓核细胞中Ⅱ型胶原蛋白和聚蛋白多糖表达,其对髓核细胞的影响可通过调控miR-190a-3p实现。关于lncRNA FAM83H-AS1对髓核细胞增殖和ECM的调控,Wei等[53]报道lncRNA FAM83H-AS1在IDD患者髓核细胞及IL-1β和TNF-α诱导的髓核细胞中表达上调,FAM83H-AS1可通过调控Notch1促进髓核细胞增殖和ECM降解。Jiang等[54]在经晚期糖基化终产物处理建立的IDD模型大鼠髓核细胞中发现FAM83H-AS1表达降低,过表达FAM83H-AS1可促进髓核细胞增殖,降低ADAMTS-4和MMP-3蛋白表达水平,抑制ECM降解。此外,Wang等[55]发现lncRNA TRPC7-AS1通过发挥ceRNA的作用,解除miR-4769-5P对HPN的抑制,促进髓核细胞ECM分解和衰老。Du等[56]报道lncRNA NR2F1-AS1可作为ceRNA,抑制miR-145-5P的表达来上调FOXO1通路以促进髓核细胞凋亡和ECM降解。通过lncRNA调控椎间盘内MMPs和ADAMTSs成员的表达来调控ECM降解,同时调控Ⅱ型胶原蛋白和聚蛋白多糖表达来维持椎间盘内ECM的合成与分解平衡,可对延缓IDD起积极作用。有关参与调控椎间盘内ECM的lncRNA及相关靶基因或通路见图3。

6 lncRNA调控椎间盘内细胞自噬

自噬是一种溶酶体参与细胞内降解途径,通过自噬泡与溶酶体结合来降解老化、损伤的细胞器以及错误折叠的蛋白,从而产生新的氨基酸和能量,来参与细胞的各种生理和病理过程[57-58]。同时自噬与凋亡密切相关,对于维持细胞稳态和完整性至关重要[59]。有报道称适当的自噬激活可保护髓核细胞,而自噬功能障碍则可促进髓核细胞死亡[60]。

连建根[59]对SD大鼠椎间盘损伤前后的椎间盘组织进行lncRNA高通量测序,发现LOC102546544、LOC102555011、LOC103692122、LOC103692949、LOC108348887及LOC108350343在椎间盘损伤组织中显著下调,这些lncRNA可能通过调节AMPK信号通路参与自噬。Zhang等[61]报道HOTAIR在IDD患者髓核细胞中高表达,其可通过miR-148a/PTEN轴促进髓核细胞自噬和凋亡。Zhan等[62]报道HOTAIR通过调节AMPK/mTOR/ULK1通路激活髓核细胞自噬,进而促进髓核细胞凋亡、衰老和ECM分解。Sun等[63]报道H19在IDD大鼠髓核细胞中表达升高,H19作为ceRNA,黏附miR-139-3p以抑制CXCR4表达,从而激活NF-κB通路来促进髓核细胞自噬和凋亡。



↑:上调;↓:下调;+:促进ECM降解;−:抑制ECM降解

图3 参与调控椎间盘内ECM的lncRNA及相关靶基因或通路

7 lncRNA调控椎间盘内炎症因子

炎症因子可导致椎间盘内发生免疫炎症反应,加速椎间盘内ECM分解,同时还可作为衰老因子,加速髓核细胞衰老[64]。TNF-α和IL-1β在炎症反应的起始和持续中起关键作用,在IDD组织中经常检测到TNF-α、IL-1β、IL-1α、IL-6、IL-17等表达水平升高[40,64]。关于lncRNA调控炎症因子,Li等[18]报道在髓核细胞中敲低lnc00917可降低促炎因子IL-6、TNF-α和IL-1β的释放。Che等[9]报道,OIP5-AS1敲低可显著抑制脂多糖诱导的髓核细胞中IL-6、TNF-α和IL-1β表达并促进IL-10的表达,同时敲低OIP5-AS1可促进髓核细胞增殖,并抑制细胞凋亡、ECM降解;该研究发现OIP5-AS1对髓核细胞的影响是通过调控miR-25-3p实现的。Chen等[65]报道,lnc01121可作为ceRNA黏附miR-150-5p以提高其下游靶基因MMP-16的表达,从而促进髓核细胞中IL-6、TNF-α和IL-1β的表达。Deng等[66]发现IDD患者髓核细胞中lncRNA ZFAS1表达较对照组明显上调,且lncRNA ZFAS1的表达与TNF-α、IL-1β和IL-6 mRNA及蛋白水平呈正相关,与IL-10 mRNA及蛋白水平呈负相关,提示lncRNA ZFAS1可能是IDD中的促炎基因。通过lncRNA调控炎症因子来抑制炎症的发生发展,将有利于改善椎间盘内的微环境,减少炎症刺激对IDD的影响。

8 lncRNA调控IDD其他方面

lncRNA可调控IDD中髓核细胞焦亡。Yang等[67]报道,lncRNA MIR155HG可作为ceRNA,黏附miR-223-3p以促进NLRP3的表达,导致髓核细胞焦亡。Li等[18]报道,敲低lnc00917可通过靶向miR-149-5p/NLRP1轴抑制髓核细胞焦亡。与此同时,已有科研人员通过病毒、可注射水凝胶及外泌体等载体将调控IDD的非编码RNA转导到动物椎间盘细胞来延缓IDD[68],但是这些载体的稳定性、应用的广泛性还需要进一步研究。

9 总结与展望

目前,lncRNA参与调控IDD的研究取得了很大进展,相当多的lncRNA在IDD中起到重要调控作用。本文总结了相关lncRNA可作为ceRNA,与其miRNA的下游目标mRNA竞争性结合miRNA,通过调节miRNA的目标mRNA表达水平及相关通路来抑制或加速IDD,这样的调节机制研究模式为我们在细胞及分子水平上了解IDD提供了更加明确的思路。单个lncRNA可参与IDD的多个病理过程,又可通过不同通路进行调控,如HOTAIR通过miR-148a/PTEN轴促进髓核细胞自噬和凋亡,又可通过调节AMPK/mTOR/ULK1通路激活髓核细胞自噬。对于同一个miRNA,可有不同的lncRNA作为ceRNA与之结合来调节IDD,如HCG18和SLC20A1-1均可作为ceRNA下调髓核细胞中miR-146a-5p表达,上调TRAF6表达以促进髓核细胞凋亡。值得注意的是,有些lncRNA不充当ceRNA,而是直接结合相应的稳定miRNA,增强其miRNA表达从而调控IDD,如lncRNA MT1DP可直接结合稳定miR-365从而提高miR-365水平,促进髓核细胞凋亡。此外,多数研究探讨lncRNA对髓核的调控,而有关lncRNA对软骨终板和纤维环的调控研究较少。未来可进一步明确lncRNA对纤维环的调控,同时探究lncRNA对软骨终板退变的调控,为延缓IDD提供更多思路。

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