非编码RNAs在心肌纤维化中的研究进展

庄宇婷[1,4], 吕延杰[1,3], 潘振伟[1,2*]

(1. 哈尔滨医科大学药学院, 黑龙江 哈尔滨 150081; 2. 中国医学科学院寒地慢病研究创新单元, 黑龙江 哈尔滨 150081; 3. 黑龙江省医学科学院中国北方转化医学研究与合作中心, 黑龙江 哈尔滨 150081; 4. 哈尔滨医科大学附属肿瘤医院科研中心, 黑龙江 哈尔滨 150081)

摘要: 心肌纤维化是多种心血管疾病的重要病理特征和改变, 包括心肌梗死和心衰等。目前, 心肌纤维化的分子机制尚不明确, 且无有效的治疗药物。非编码RNAs是一类不具有编码蛋白能力的RNAs, 可以在转录调控、转录后调控和表观遗传学水平影响基因的表达, 参与细胞的生物学过程。非编码RNAs通过影响心脏成纤维细胞增殖和转化等过程参与心肌纤维化的调控, 可作为心肌纤维化的潜在干预靶点和生物标记物, 为心肌纤维化相关疾病的治疗提供新的策略和方法。本文旨在对非编码RNAs在心肌纤维化中的功能和机制的研究进展进行综述。

关键词: 非编码RNA; 基因调控; 心肌纤维化; 生物标记物; 分子机制

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Research progress of noncoding RNAs in cardiac fibrosis

ZHUANG Yu-ting[1,4], LÜ Yan-jie[1,3], PAN Zhen-wei[1,2*]

(*1. College of Pharmacy, Harbin Medical University, Harbin 150081, China; 2. Research Unit of Noninfectious Chronic Diseases in Frigid Zone, Chinese Academy of Medical Sciences, Harbin 150081, China; 3. China Northern Translational Medicine Research and Cooperation Center, Heilongjiang Academy of Medical Sciences, Harbin 150081, China; 4. Scientific Research Center, Harbin Medical University Cancer Hospital, Harbin 150081, China*)

Abstract: Cardiac fibrosis is a vital pathological feature of various cardiovascular diseases, including myocardial infarction and heart failure. However, there have been few clinical interventions to treat cardiac fibrosis. Noncoding RNAs (ncRNAs) are a class of RNAs that do not encode proteins. ncRNAs participate in various cellular biological processes and regulate gene expression at transcription, post-transcription and epigenetic levels. Recent studies demonstrate that ncRNAs participate in the regulation of cardiac fibrosis by affecting the proliferation and transition of cardiac fibroblasts. ncRNAs can be used as potential intervention targets and biomarkers for cardiac fibrosis, provide new strategies and approach for treating and preventing fibrosis associated cardiovascular diseases. This review summarizes the function and mechanisms of ncRNAs in cardiac fibrosis.

Key words: noncoding RNA; gene regulation; cardiac fibrosis; biomarker; molecular mechanism

心肌纤维化是多种心脏疾病发展到一定阶段的共同病理特征, 是心室重构的关键诱因。在缺血或长期压力负荷等状态下, 心肌成纤维细胞 (cardiac fibroblasts, CFs) 增殖并活化, 向肌成纤维细胞转化, 持续过量合成生长因子、细胞因子、趋化因子和细胞外基质 (extracellular matrix, ECM) 等, 使ECM过度沉积, 导致心脏传导异常、心脏收缩功能减弱、心室壁硬化和顺应性降低, 最终诱发心衰。

非编码RNAs (noncoding RNAs, ncRNAs) 是一类不编码蛋白的RNAs, 在人类基因组中约占98%, 种类繁多, 主要的功能ncRNAs包括微小RNAs (microRNAs, miRNAs)、长链非编码RNAs (long noncoding RNAs,

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*通讯作者 Tel: 86-451-86671354, E-mail: panzw@ems.hrbmu.edu.cn
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lncRNAs) 和环状RNAs (circular RNAs, circRNAs) 等。ncRNAs参与细胞周期、细胞分化和凋亡等细胞生命活动及疾病过程的调控, 是心血管疾病的重要调节因子。研究发现, 众多ncRNAs在心肌纤维化组织中出现差异表达, 表明其参与心肌纤维化发生和发展的可能性, ncRNAs通过多层面的复杂机制调控心肌纤维化过程, 评价和探讨它们作为心肌纤维化生物标记物和治疗靶点的潜力将为心肌纤维化的临床诊断和治疗提供新策略。本文旨在对ncRNAs的作用机制和在心肌纤维化中的研究进展进行综述。

1 miRNAs

1.1 miRNAs及其作用机制

miRNAs是一类长度约22 nt的小分子单链ncRNA, 具有高度的保守性。miRNAs主要位于基因间隔区和蛋白编码区的内含子中。miRNAs经复杂的剪切加工而成: 首先, 由RNA聚合酶II转录形成初级转录产物 (pri-miRNAs) 后, 在Dorsha作用下生成前体miRNAs (pre-miRNAs); 随后, pre-miRNAs由exportin-5和Ran-GTP从细胞核转运至细胞质中, 被RNA聚合酶III Dicer识别剪切成长度为20～25 nt的双链miRNAs。最后, 双链miRNAs在Ago的作用下与RNA诱导的沉默复合体 (RISC) 结合, 其中一条链被降解, 而另一条链形成成熟的miRNAs[1,2]。

miRNAs经典的作用机制为: miRNAs的种子区通过碱基互补配对的方式与靶mRNA的3'非翻译区 (3' UTR) 结合, 诱导靶mRNA降解或抑制其翻译。miRNAs可调控超过60%蛋白质编码基因的翻译[3]。这种作用的特点是: 单个miRNA可以靶向多个mRNAs, 而不同的miRNAs也可共同调控同一个靶基因[4]。近期研究报道, Han等[5]发现miRNA-711的核心序列 (非种子区) 与瞬时受体电位锚定蛋白1 (TRPA1) 结合, 使少量Ca^{2+}进入神经, 与淋巴瘤小鼠瘙痒的产生相关。Yang等[6]发现miRNA-1的核心序列 (非种子区) 与内向整流钾通道Kir2.1结合, 抑制了钾电流I_{K1}, 提高细胞传导速度, 降低心律失常发生。此为miRNAs的另一调控机制, 即miRNAs可以与蛋白直接结合而调控其功能。miRNAs的异常表达伴随心肌纤维化的发生和发展, 但目前的研究集中于miRNAs靶向mRNAs的3' UTR调控心肌纤维化。

1.2 miRNAs与心肌纤维化

1.2.1 miR-21与心肌纤维化 miR-21是一类压力反应型的成纤维细胞富集的miRNA, miR-21在多种纤维化相关的心脏疾病中表达显著升高[7-10], 可作为心肌纤维化的生物标记物[11]。转化生长因子β (TGF-β) 信号通路是miR-21的主要靶点。TGF-β III型受体 (TGFβRIII) 通过抑制TGF-β1和p-Smad3的表达发挥抗心肌纤维化的作用。Liang等[12]研究发现TGFβRIII是miR-21的直接靶点, miR-21抑制其表达, 促进心肌纤维化。Smad7是miR-21的另一靶点, Smad7抑制Smad2和Smad3的激活起到抗心肌纤维化的作用[10]。Watanabe和Li等[8,13]证实miR-21在Ang II诱导的心肌纤维化模型中表达升高, 且分别通过靶向程序性细胞死亡因子4 (PDCD4) 和软脂酰化磷蛋白Sprouty1 (Spry1) 对Ang II正反馈调节, 激活转录激活蛋白1 (AP-1)/TGF-β1和细胞外信号调节激酶 (ERK)/TGF-β/Smad通路促进心肌纤维化。此外, Dong等[14]在研究熊果酸抗心肌纤维化的机制时发现, 熊果酸抑制miR21/ERK通路。miR-21还通过靶向Jagged1, 发挥促进大鼠心肌成纤维细胞向肌成纤维细胞转化和心肌纤维化, 导致心脏功能障碍[15]。

miR-21在房颤患者心脏中表达升高, Tao等[16]采用人成纤维细胞进行实验研究, 结果显示下调miR-21后, WW结构域结合蛋白1 (WWP-1) 表达升高, 抑制成纤维细胞增殖, 减轻心房纤维化。Cao等[17]发现miR-21通过抑制细胞黏附分子1 (CADM1) 的表达激活信号转导和转录激活因子3 (STAT3) 通路, 发挥促房颤和心肌纤维化的作用。

Hinkel等[18]首次报道了抑制miR-21对大型动物心衰的治疗作用, 在猪心肌缺血再灌注损伤 (I/R) 模型构建后的第5天注射LNA-antimiR-21, 模型后33天检测发现沉默miR-21可减轻心肌肥厚和心肌纤维化并改善心脏功能, 为抑制miR-21对心衰治疗的可行性提供了依据。

1.2.2 miR-29家族与心肌纤维化 miR-29家族包含miR-29a、miR-29b和miR-29c, 它们有相同的保守种子区, 在不同动物组织中发挥抗纤维化的作用, 且它们的靶点相似[19], 但在CFs和心肌细胞中的miR-29对心肌纤维化的调控作用截然相反。CFs中的miR-29家族具有抗心肌纤维化的作用, 在小鼠和人梗死的心肌边缘区组织以及TGF-β作用的CFs中表达显著降低, 过表达miR-29通过靶向I型胶原α1 (COL1A1)、COL1A2、COL3A1、弹性蛋白和原纤维蛋白抑制胶原合成[20]。Zhang等[21]研究发现, 敲除白介素-6 (IL-6) 可缓解糖尿病小鼠的心肌纤维化, 并改善心脏功能, 其机制包括抑制miR-29/TGF-β通路。miR-29还可通过靶向周期蛋白依赖性激酶2 (CDK2) 抑制CFs增殖和胶原合成, 发挥抗心肌纤维化的作用[22]。

而Sassi等[23]研究发现, 心肌细胞中的miR-29家族具有促心肌纤维化和心肌肥厚的作用。特异性敲除心肌细胞中的miR-29可减轻小鼠心肌肥厚和心肌纤维化, 机制为miR-29靶向抑制糖原合酶激酶3B (GSK3B)、

连环蛋白β相互作用蛋白1 (CTNNBIP1)、HMG盒转录因子1 (HBP1) 和GLIS家族锌指蛋白2 (GLIS2) 并激活Wnt和活化T细胞核因子 (NFAT) 通路。

在犬充血性心衰诱导的心房纤维化中, miR-29在心房组织和心房成纤维细胞中表达显著降低, 且其在慢性房颤的患者心房中表达也显著降低, 过表达miR-29靶向抑制COL1A1、COL3A1和原纤维蛋白[24]。

1.2.3 miR-133a与心肌纤维化 miR-133是心脏中高表达的miRNA, 在心肌纤维化模型中表达降低, 并与COL1A1 mRNA的3' UTR直接结合减轻心肌纤维化[25]。在小鼠糖尿病心肌病模型中, miR-133a下调纤连蛋白1 (FN1) 和COL4A1的表达, 抑制ERK1/2和Smad2的磷酸化预防糖尿病的早期心肌纤维化[26]。miR-133a还可通过抑制蛋白激酶B (Akt)、TGF-β1和结缔组织生长因子 (CTGF) 减轻心肌纤维化并改善心脏功能[27,28]。

尼古丁可引发心房重构导致房颤, Shan等[29]发现给予尼古丁的犬miR-133和miR-590表达显著降低, 而它们的靶点TGF-β1和TGF-βRII表达明显升高。

凋亡酶激活因子1 (Apaf-1) 是miR-133a的另一靶点, 将转染了miR-133a的骨髓间充质干细胞转移入梗死的大鼠心脏后, 抑制Apaf-1的表达, 改善大鼠心脏功能, 减轻梗死后的心肌纤维化, 且重编程miR-133a拟似物的干细胞在移植后凋亡减少, 移植效率更高, 提高了干细胞移植治疗心血管疾病的临床价值[30]。

1.2.4 MyomiRs家族与心肌纤维化 miR-208a、miR-208b和miR-499是肌球蛋白基因内含子编码的miRNA家族 (MyomiRs)。内皮素是miR-208a调控心肌纤维化的重要靶点, miR-208a促进内皮素的表达、加重机械张力和容量超负荷心衰诱导的心肌纤维化[31,32]。miR-208a敲除小鼠减轻了胸主动脉结扎 (TAB) 引发的心肌肥厚和心肌纤维化[33]。心血管疾病是慢性肾病患者, 特别是慢性透析患者发病和死亡的主要原因, 甲状腺激素与心肌肥厚和心肌纤维化关系密切, Prado-Uribe等[34]研究发现miR-208参与慢性肾病大鼠甲状腺激素减少和心肌纤维化的调控。

miR-499在心衰的患者心脏组织中表达升高, 过表达miR-499引起小鼠心肌肥厚和纤维化。全基因组RISC和RNA测序发现miR-499有67个直接靶点, 包括Akt和丝裂原活化蛋白激酶 (MAPKs)[35]。Shieh等[36]发现miR-499促心肌肥厚、纤维化和损伤心脏功能的作用呈剂量依赖性, 全基因表达谱分析发现miR-499转基因小鼠中即刻早期应答基因出现差异表达, 如早期生长反应因子-1 (Egr1)、早期生长反应因子-2 (Egr2)、原癌基因 (Fos)、β肌球蛋白重链 (Myh7) 和骨骼肌肌动蛋白 (Acta1) 等, 说明miR-499至少通过调控即刻早期应答基因触发心脏反应。

1.2.5 miR-328与心肌纤维化 Du等[37]研究发现, CFs中的miR-328与TGF-βRIII直接结合, 促进TGF-β1信号通路, 沉默miR-328减轻心肌梗死 (MI) 诱发的心肌纤维化。随后, 该团队发现心肌细胞特异性过表达miR-328通过激活TGF-β1信号通路促进胶原合成、加重纤维化, 将过表达miR-328的心肌细胞与CFs共培养后, CFs中miR-328表达也升高, 引起CFs出现纤维化表型, 而这一促纤维化作用可通过抑制CFs中的miR-328抵消[38]。

此外, miR-101在大鼠MI模型中表达降低, 过表达miR-101通过抑制原癌基因c-Fos及其下游的TGF-β1减轻心脏间质纤维化[39], 弗林蛋白 (furin) 是TGF-β1的上游因子, miR-24抑制furin进而下调TGF-β1的表达, 减轻心肌纤维化[40]。miR-22与微囊蛋白-3 (Cav-3) 结合, 促进蛋白激酶Cε (PKCε) 的活化, 促进心肌纤维化[41]; miR-22在衰老的心脏中表达升高, 促进CFs衰老和活化, 参与衰老相关的心肌纤维化的调控[42]。miR-503通过apelin-13-TGF-β-CTGF通路促进CFs增殖和胶原合成, 发挥促心肌纤维化的作用[43]。多个miRNAs参与调控心肌纤维化的过程 (表1)[8,10,12-17,20-32,37-77], 表明miRNAs是心肌纤维化的重要调控因子, 具有成为心肌纤维化治疗靶点的潜能。

1.3 外泌体miRNAs调控心肌纤维化

外泌体miRNAs (exo-miRNAs) 因受到外泌体的保护而稳定存在于组织和体液中, 免于被核酶降解, 通过旁分泌途径参与疾病的调控或作为生物标记物。近年来, exo-miRNAs对心肌纤维化的调控作用吸引了研究者的目光。Ferguson等[78]对间充质干细胞来源的外泌体进行miRNAs表达谱的分析发现, 有23个miRNAs高表达, 且生物信息学分析结果显示它们的靶点包括纤维化相关通路, 如Wnt、血小板衍生生长因子 (PDGF) 和TGF-β信号通路。用含有间充质干细胞来源外泌体的培养基培养人成纤维细胞12 h后出现剂量依赖性抑制TGF-β1诱导的COL1合成, 证实了exo-miRNAs对心肌纤维化的调控作用。Wang等[49]向胫骨前肌注射exo-miR-26a后发现患有慢性肾病的小鼠心脏中miR-26a表达升高, 心肌纤维化减轻, 心脏功能改善, 其机制为exo-miR-26a抑制叉头框蛋白O1 (FoxO1) 活性并降低COL1A1和CTGF的表达。研究运动减轻糖尿病心血管并发症的分子机制时发现, 运动可增加心肌细胞来源的exo-miR-29和exo-miR-455含量, 抑制基质金属蛋白酶9 (MMP9) 活性, 减轻心肌纤维化[79]。心肌细胞来源的exo-miR-208抑制双特异性酪氨酸磷酸化调控激酶2 (Dyrk2) 的表达和NFAT的磷酸化, 促进NFAT核

Table 1 miRNAs with implication in cardiac fibrosis. AF: Atrial fibrillation; Akt: Protein kinase B; Apaf-1: Apoptotic protease activating factor-1; AMI: Acute myocardial infarction; Ang II: Angiotensin II; AR: Androgen receptor; CADM1: Cell adhesion molecule 1; CDK6: Cyclin-dependent kinase 6; CKD: Chronic kidney disease; COL1A1: Collagen-1A1; COL3A1: Collagen-3A1; CTGF: Connective tissue growth factor; CTNNBIP1: Catenin-beta interacting protein 1; EGR1: Early growth response 1; FBW7: F-box and WD repeat domain-containing 7; FoxO1: Forkhead box O1; GLIS2: GLIS family zinc finger 2; GRB2: Growth factor receptor-bound protein 2; GSK3B: Glycogen synthase kinase-3 beta; HBP1: HMG box transcription factor 1; HF: Heart failure; HG: High glucose; ISO isoprenaline; MI: Myocardial infarction; MKK6: Mitogen-activated protein kinase kinase 6; PDCD4: Programmed cell death 4; PTAFR: Platelet-activating factor receptor; TAC: Transverse aortic constriction; TGF-β1: Transforming growth factor beta 1; TGFβR1: Transforming growth factor beta receptor 1; THBS1: Thrombospondin 1; TSP-1: Thrombospondin-1; SFRP5: Secreted frizzled-related protein 5; SIRT1: Silent mating type information regulation 2 homolog 1; STZ: Streptozotocin; WWP-1: WW domain-containing protein 1

miRNA	Stimulation	Target gene	Pro-/anti-fibrotic	Reference
miRNA-1	Ang II	Cyclin D2, CDK6	Anti	[44]
miRNA-15a/b	Type 2 diabetes	TGFβR1, CTGF	Anti	[45]
miRNA-18a,19a/b	Aged	CTGF, TSP-1	Anti	[46]
miR-24	MI	Furin	Anti	[40,47,48]
miR-26a	CKD	FoxO1	Anti	[49]
miR-29b	Ang II, AMI, STZ, AF	TGF-β1, collagens, fibrillins, elastin, CDK2, COL1A1, COL3A1	Anti	[20-22,24,50]
miR-29b-3p	TGF-β1	FOS	Anti	[51]
miR-30a	MI	CTGF	Anti	[52]
miR-30c	TAC	CTGF	Anti	[53]
miR-30e	ISO	Snai1	Anti	[54]
miR-101a	MI/Ang II, MI/hypoxia	c-Fos, TGFβRI	Anti	[39,55]
miR-133	TAC, STZ, ISO, Ang II, AF, HF, AMI, MI	CTGF, TGFβ1, COL1A1, TGF-βRII, Akt, Apaf-1	Anti	[25-30,53,56]
miR-378	TAC, MI	MKK6, GRB2	Anti	[57,58]
miR-455	TAC	Calreticulin	Anti	[59]
miR-1954	Ang II	THBS1	Anti	[60]
let-7d	MI	PTAFR	Anti	[61]
miR-21	Ang II/TAC, MI, AF	PDCD4, Smad7, ERK, Jagged1, WWP-1, CADM1	Pro	[8,10,14-17]
miR-21-3p	TAC, MI, STZ	SPRY1, TGFβRIII, AR	Pro	[12,13,62,63]
miR-22	MI, aged	Cav3, mimecan	Pro	[41,42,64]
miR-27b	MI/Ang II	FBW7	Pro	[65]
miR-29	TAC	GSKB3, CTNNBIP1, HBP1, GLIS2	Pro	[23]
miR-34	MI/TAC	Sema4b	Pro	[66]
miR-34a	MI, doxorubicin	Smad4, Bcl2, SIRT1	Pro	[67,68]
miR-150-5P	Ang II	EGR1	Pro	[69]
miR-125b	TAC, MI	p53, SFRP5	Pro	[70,71]
miR-155	TAC, HG	Jarid2, TGF-β	Pro	[72,73]
miR-199b-5p	MI	Dyrk1a	Pro	[74]
miR-208a	Volume-overload, mechanical stretch, HF	Endoglin, Myh7	Pro	[31,32,75,76]
miR-327	Ang II	Integrin β3	Pro	[77]
miR-328	MI	TGF-βRIII, TGF-β	Pro	[37,38]
miR-503	Ang II	Apelin 13	Pro	[43]

转位, 核NFAT促进心CFs中CTGF、COL1A1、COL3A1和α-平滑肌肌动蛋白 (α-SMA) 的表达, 从而诱导心肌纤维化[80]。

目前, exo-miRNAs的长期治疗效果还未见报道, exo-miRNAs的细胞靶向性有待提高, 其调控心肌纤维化的机制仍需进一步研究。

2 lncRNAs

2.1 lncRNAs及其功能

lncRNAs是一类长度大于200 nt的ncRNAs, 约占全部ncRNAs的80%～90%, 在哺乳动物中表达丰富且种类较多。根据它们与邻近编码区基因组的相对位置关系, 可以分为5种类型: 正义lncRNAs、反义lncRNAs、基因间lncRNAs、内含子lncRNAs和双向lncRNAs。保守性低是大部分lncRNAs的特点, 比对人和小鼠的序列后发现, lncRNAs只有20%同源基因, 限制了其临床应用潜能, 但lncRNAs结构复杂, 包含一级结构和高级结构, 一级结构保证其可以通过碱基互补配对的方式调控基因表达; 二级结构和三级结构大多较为保守,

对lncRNAs发挥功能至关重要; 更高级结构则因受到技术手段等因素的限制研究较少。lncRNAs可通过与DNAs、RNAs和蛋白结合参与表观遗传学、转录和转录后水平的调控[81]。

2.2 lncRNAs与心肌纤维化

Qu等[82]构建小鼠MI模型诱导心肌纤维化, 并通过芯片检测发现545个lncRNAs的表达发生明显改变, 且生物信息学分析结果显示差异表达的lncRNAs与纤维化相关基因关系密切, 说明lncRNAs在心肌纤维化调控中扮演重要角色, 吸引了研究者对lncRNAs调控心肌纤维化进行研究。

2.2.1 lncRNAs与DNAs相互作用调控心肌纤维化

目前, lncRNAs与DNAs直接结合调控心肌纤维化的研究较少。已报道的有保守型结直肠肿瘤差异表达lncRNA (lncRNA Crnde) 与心肌纤维化标记基因负性相关, Smad3转录激活Crnde, Crnde则竞争性抑制Smad3与TGF-β靶基因启动子的SBE DNA结合, 抑制Smad3与α-SMA基因启动子的结合, 减少CFs向肌成纤维细胞转化, 发挥抗心肌纤维化的作用[83]。成纤维细胞生长因子9 (FGF9) 是纤维化的抑制剂并可下调TGF-β信号通路, FGF9和FGF9相关因子lncRNA (lncRNA FAF) 位于同一条染色体上, 且FGF9上游启动子区255 bp与lncRNA FAF反向互补, lncRNA FAF可作为转录因子促进FGF9表达, 抑制TGF-β1的分泌, 下调磷酸化Smad2/3表达, 减轻心肌纤维化[84]。

2.2.2 lncRNAs与RNAs相互作用调控心肌纤维化

lncRNAs作为miRNAs的竞争性内源RNAs (ceRNAs) 调控心肌纤维化是研究最广泛的作用机制, 且CFs是心肌纤维化的主要效应细胞。H19是第一个被发现的lncRNA, 也是目前研究最全面的lncRNA, 具有高度的保守性。H19可作为内源性分子海绵调控心肌纤维化的发生和发展, 已有研究H19通过miR-455/CTGF信号通路促进Ang II诱导的心肌纤维化[85]。肺腺癌转录本1 lncRNA (lncRNA MALAT1) 在MI心脏和Ang II处理的CFs中表达升高, 敲减MALAT1减轻MI引起的心功损伤, 减少Ang II诱导的细胞增殖和胶原合成, 其稳定性和TGF-β1活性受miR-145调控[86]。在急性MI模型中, X-失活特异性转录本lncRNA (lncRNA XIST) 通过吸附miR-155-5p促进CFs增殖和ECM积聚[87]。此外, 作者所在团队发现MI相关转录本lncRNA (lncRNA MIAT)、促纤维化lncRNA (PFL) 和促心肌纤维化lncRNA (PCFL) 充当ceRNAs, 作用于CFs, 发挥促心肌纤维化的作用。lncRNA MIAT竞争性结合miR-24, 减弱其对furin和TGF-β1的抑制作用, 敲减MIAT以减轻心肌纤维化并改善心功[48]。lncRNA PFL竞争性结合let-7d, 抑制其表达和抗纤维化活性, 上调促纤维化蛋白血小板活化因子受体 (PTAFR) 的表达, 促进CFs增殖和向肌成纤维细胞转化, 由此加重心肌纤维化和心脏功能障碍[61]。lncRNA PCFL是另一个促心肌纤维化因子, PCFL充当miR-378的“海绵”, miR-378通过抑制靶基因生长因子受体结合蛋白2 (GRB2) 发挥抗心肌纤维化的作用。过表达PCFL加重MI诱导的心肌纤维化和心功损伤[58]。

lncRNAs不仅调控CFs的增殖和分化, 还可调控CFs及其他心脏细胞的生物学过程, 从而影响心肌纤维化的发生和发展, 如凋亡和焦亡等。Yang等[88]发现Kcnq1重叠转录本1 lncRNA (lncRNA Kcnq1ot1) 通过miR-214-3p/caspase-1/TGF-β1信号通路参与糖尿病心肌病的调控, 高糖条件下沉默Kcnq1ot1下调caspase-1的表达, 促进IL-1β的分泌, 由此抑制TGF-β1/Smads信号通路, 改善心脏功能和心肌纤维化, 减轻CFs焦亡。核苷酸结合寡聚化结构域样蛋白3 (NLRP3) 炎症小体是伴有心衰的室性心律失常 (VA-HF) 的重要调控因子, SOX2覆盖转录本lncRNA (lncRNA SOX2-OT) 通过吸附miR-2355-3p促进NLRP3的表达, 沉默SOX2-OT抑制NLRP3、caspase-1、IL-1β和TGF-β1的表达并减少活性氧的生成, 减轻VA-HF大鼠心肌细胞坏死和心肌纤维化, 改善心脏功能[89]。lnc_000898通过miR-375/磷酸肌醇依赖性蛋白激酶-1 (PDK1) 轴减轻MI后的心肌细胞凋亡、心肌纤维化并改善心脏功能[90]。lncRNA MIAT靶向miR-133a-3p加重房颤导致的心肌细胞凋亡和心肌纤维化, 增加纤维化相关基因COL1、COL3、CTGF和TGF-β1的表达[91]。

2.2.3 lncRNAs与蛋白相互作用调控心肌纤维化

lncRNAs与蛋白相互作用是其调控心肌纤维化的另一主要机制。lncRNAs可与蛋白分子直接结合影响其定位、代谢及活性。母系表达基因3 lncRNA (lncRNA Meg3) 在成纤维细胞中高表达, Piccoli等[92]使用GapmeR介导Meg3的沉默后, 破坏Meg3与p53之间的相互作用, p53与MMP2启动子的结合被抑制, MMP2表达降低, 减轻主动脉缩窄 (TAC) 导致的心肌纤维化和心脏扩张功能障碍。H19除了作为ceRNAs调控心肌纤维化, 还可通过与蛋白相互作用发挥功能, Y盒结合蛋白-1 (YB-1) 是COL1A1的抑制剂, Choong等[93]发现H19作为YB-1的拮抗剂, 抑制YB-1的功能, 恢复COL1A1的表达, 促进心肌纤维化。lncRNA KCNQ1OT1直接靶向肉瘤融合蛋白 (FUS) 并抑制其表达, 减轻多柔比星诱导的心衰、减少心肌细胞凋亡并减小心肌纤维化面积[94]。

TGF-β/Smads信号通路在心肌纤维化的发生和发展中发挥重要作用。Zhang等[95]发现另一个成纤维细胞高表达的心肌成纤维细胞相关转录本lncRNA (lncRNA

CFAST) 在MI模型中表达显著升高, CFAST竞争性地抑制毛状样蛋白1 (COTL1) 与转化生长因子β受体相关蛋白1 (TRAP1) 结合, 增加Smad2/Smad4复合物的形成以增强TGF-β信号, 促进CFs活化。lncRNA GASS与Smad3结合并促进其与Smad3去磷酸化酶PPM1A结合, 加速Smad3的去磷酸化, 抑制TGF-β/Smad3信号通路, 抑制CFs活化从而减轻心肌纤维化[96]。

lncRNAs还可通过与蛋白结合调控基因转录影响心肌纤维化。lncRNA MALAT1可增加动脉平滑肌细胞活性并促进其增殖, 引发自发性高血压大鼠重度心肌纤维化, 机制为lncRNA MALAT1招募Suv39h1到成肌分化抗原 (MyoD) 的结合位点, 引起靶基因的H3K9me3三甲基化和表达降低, 抑制MyoD的转录[97]。作者所在团队最新研究报道了支架附着因子B相互作用lncRNA (lncRNA SAIL) 与支架附着因子B (SAFB) 结合后并未影响其表达, 而是阻断SAFB与RNA聚合酶II的相互作用, 抑制纤维化相关基因的转录, 从而发挥抗心肌纤维化的作用, 且人源保守的SAIL片段 (hSAIL) 显著抑制CFs增殖和胶原合成[98]。

lncRNAs的功能广泛、作用机制复杂, 调控心肌纤维化的研究众多 (表2)[48,58,61,83-116]。目前, 已有多篇报道lncRNAs影响蛋白的表达或功能, 从而调控心肌纤维化相关病理过程, 但其调控蛋白的具体机制并未阐明, 仍需要进一步研究。作者所在团队发现细胞质中的lncRNA 30245通过抑制过氧化物酶体增殖物激活受体γ (PPAR-γ) 后上调CTGF的表达, 促进CFs增殖和胶原合成, 但lncRNA 30245与PPAR-γ未见直接结合[116]。IL-17通过lncRNA AK081284调控糖尿病小鼠心肌纤维

Table 2 lncRNAs with implication in cardiac fibrosis. ADR: Doxorubicin; AT1: Angiotensin II type 1 receptor; CFAST: Cardiac fibroblast-associated transcript; COTL1: Coactosin-like 1; Crnde: Colorectal neoplasia differentially expressed; DUSP5: Fual-specificity phosphatase 5; EZH2: Enhancer of zeste homolog 2; E2F1: E2F transcription factor 1; FAF: FGF9-associated factor; Fendrr: FOXF1 adjacent non-coding developmental regulatory RNA; FGF9: Fibroblast growth factor 9; FUS: Fused in sarcoma; GAS5: Growth arrest-specific 5; KCNQ1OT: KCNQ1 opposite strand/antisense transcript 1; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; Meg3: Maternally expressed gene 3; MIAT: Myocardial infarction associated transcript; MIRT1: Myocardial infarction associated transcript 1; MMP2: Matrix metalloprotease-2; NF-κB: Nuclear factor kappa B; PAH: Pulmonary arterial hypertension; PCFL: Pro-cardiac fibrotic lncRNA; PFL: Pro-fibrotic lncRNA; PTEN: Phosphatase and tensin homologue; RMRP: RNA component of mitochondrial RNA processing endoribonuclease; SAFB: Scaffold attachment factor B; SAIL: Scaffold attachment factor B interacting lncRNA; SHRs: Spontaneously hypertensive rats; Wisper: Wisp2 super-enhancer-associated RNA; YB-1: Y-box-binding protein-1; ZFAS1: Zinc finger antisense 1

lncRNA	Stimulation	Target gene	Pro-/anti-fibrotic	Reference
Crnde	STZ	Smad3	Anti	[83]
FAF	Ang II	FGF9	Anti	[84]
GAS5	ISO, TGF-β	miR-21, PTEN/MMP2, Smad3	Anti	[96,99-101]
KCNQ1OT	HG, ADR	miR-214-3p, FUS	Anti	[88,94]
SAIL	MI/TAC	SAFB	Anti	[98]
000898	MI	miR-375	Anti	[90]
Safe	MI/TGF-β1	Sfrp2	Pro	[102]
AK081284	STZ/HG	TGF-β	Pro	[103]
CFAST	MI	COTL1	Pro	[95]
Fendrr	TAC	miR-106b	Pro	[104]
H19	ISO/TGF-β1, type 2 diabetes, MI, PAH	miR-455, YB-1, DUSP5, E2F1/EZH2	Pro	[85,93,105,106]
LICPAR	Ang II	TGF-β/Smad	Pro	[107]
MALAT1	MI, STZ, SHRs	miR-145, MyoD, miR-141	Pro	[86,97,108]
Meg3	TAC	MMP2	Pro	[92]
MIAT	MI, AF	miR-24, miR-133a-3p	Pro	[48,91]
MIRT1	I/R in diabetes	NF-κB	Pro	[109]
n379519	MI	miR-30	Pro	[110]
PFL	MI	let-7d	Pro	[61]
PCFL	MI	miR-378	Pro	[58]
RMRP	Ang II	miR613	Pro	[111]
SOX2-OT	VA-HF	miR-2355-3p	Pro	[89]
Wisper	MI	COL3A1, Fn1	Pro	[112]
XIST	AMI	miR-155-5p	Pro	[87]
ZFAS1	CKD	miR-4711-5p	Pro	[113]
000908	ISO	EP4	Pro	[114]
554	MI	TGF-β1	Pro	[115]
30245	MI	PPAR-γ	Pro	[116]

化, 敲除IL-17抑制AK081284的表达, 敲减AK081284降低TGF-β的表达, 减轻糖尿病小鼠心肌纤维化并改善心功[103]。内皮间质转化 (EndMT) 作为心肌纤维化的主要诱因之一日益受到关注。lnc000908是内皮细胞富集的lncRNA, 敲减lnc000908后上调前列腺素E2受体4 (EP4) 的表达并抑制TGF-β1诱导的心脏微血管内皮细胞的内皮间质转化, 改善心肌纤维化和心脏功能[114]。预测心脏重构的lncRNA (lnc LICPAR) 在伴有窦性心律的房颤患者心房组织中表达升高, Ang II增加心房成纤维细胞中LICPAR、Col I、Col III和α-SMA的表达, 促进Smad2/3的磷酸化、细胞活性和增殖, 过表达LICPAR进一步增加Ang II的促进作用, 而敲减LICPAR则作用相反[107]。氧化应激和炎性反应也是心肌纤维化的主要发病机制, Liu等[109]研究发现敲减MI相关转录本1 lncRNA (lncRNA MIRT1) 抑制核因子κB (NF-κB) 信号通路的激活, 减轻老年糖尿病小鼠的I/R损伤, 减小心肌纤维化面积, 减少心肌凋亡, 改善氧化应激和炎性损伤。H19在肺动脉高压患者右室表达升高, 沉默H19后减弱其对E2F1/EZH2心脏保护功能的抑制, 抑制心肌细胞肥厚, 改善病理性右室肥厚、纤维化和毛细血管稀疏等症状。临床研究发现H19高表达可作为肺动脉高压的诊断和预后预测标记物[106]。

2.2.4 外泌体lncRNAs调控心肌纤维化 外泌体是lncRNAs实现细胞间交流的重要载体。Wang等[113]用人心肌细胞来源的exo-锌指蛋白反义链1 (ZFAS1) 处理人CFs后诱导成纤维细胞向肌成纤维细胞转化, 且纤维化相关标记物表达增加, 向慢性肾病小鼠尾静脉注射exo-ZFAS1后lncRNA ZFAS1与miR-4711-5p结合并促进Wnt/β catenin通路激活, 加重小鼠心功损伤和心肌纤维化。

3 circRNAs

3.1 circRNAs及其生物学功能

circRNAs是另一类功能ncRNAs, 真核细胞中的circRNAs由前体mRNAs反向剪接而成。根据来源可将circRNAs分为外显子来源的circRNAs、套索内含子来源的circRNAs和外显子−内含子来源的circRNAs。circRNAs是一类独特的ncRNAs, 不具有5'帽和3' poly (A), 其5'端和3'端以共价键的形式连接成闭合的环状结构, 使其不易被核酸外切酶降解, 更稳定、半衰期更长。研究发现circRNAs具有高度保守性, 表达具有细胞、组织、疾病和发育阶段特异性。circRNAs广泛表达于真核细胞中, 其表达量通常与同源的线性RNA相当, 但部分circRNAs的表达可超过线性RNA的10倍。

circRNAs主要有以下4种生物学功能: ① 与lncRNAs相同, circRNAs也可作为miRNAs的分子海绵, 竞争性抑制miRNAs与靶mRNAs结合, 这是目前研究最多的circRNAs的功能, 特点是: 同一个circRNA可能包含某个miRNA的多个结合位点, 也可能结合不同的miRNAs; 不同的circRNAs可同时靶向一个miRNA。另外, circRNAs与其同源的mRNAs存在序列重复, 因此可互为ceRNAs, 与靶miRNAs结合。② circRNAs可以与蛋白结合影响其活性或代谢, 或通过影响蛋白的亚细胞定位发挥功能, 还具有招募和蛋白支架的作用, 实现多基因的同时调控。③ circRNAs可通过调控亲本基因的转录或前体mRNAs的剪切调节亲本基因的表达。circRNAs还能够扭转剪切偏好, 有利于宿主基因的选择性剪切。④ 部分circRNAs具有有效的开放阅读框, 可翻译成蛋白[117,118]。

3.2 circRNAs与心肌纤维化

circRNAs在心肌分化和心血管疾病中扮演重要角色, 与心肌纤维化关系密切。Gu等[119]通过测序发现心肌纤维化中circRNAs的表达谱发生明显改变, 283个circRNAs表达出现差异, 生物信息学分析发现这些circRNAs与TGF-β、PI3K-Akt、AMPK和MAPK等纤维化相关信号通路关系密切, 说明circRNAs可作为心肌纤维化的重要治疗靶点。

3.2.1 circRNAs与miRNAs相互作用调控心肌纤维化 circRNAs竞争性结合miRNAs调控心肌纤维化是目前研究最广泛的作用机制。同源结构域相互作用蛋白激酶3 (HIPK3) circRNA (circHIPK3) 是重要的心肌纤维化调控因子, 参与多种疾病相关的心肌纤维化的调控。circHIPK3在Ang II和糖尿病诱导的心肌纤维化模型中表达显著升高, circHIPK3充当miR-29b-3p的“海绵”并上调其靶基因α-SMA、COL1A1和COL3A1, 沉默circHIPK3可抑制Ang II和糖尿病诱导的心肌纤维化[120,121]。此外, circHIPK3通过靶向miR-152-3p/TGF-β2轴促进缺氧诱导的心肌纤维化[122]。

circRNAs可调控心肌细胞病变影响心肌纤维化进程, 骨膜素circRNA (circPOSTN) 在心梗患者血浆、心梗模型小鼠和缺氧复氧处理的人心肌细胞中表达升高, 敲减circPOSTN靶向miR-96-5p/Bcl2/腺病毒E1B结合蛋白3 (BNIP3) 增加胶原蛋白、α-SMA、心钠肽 (ANP) 和脑钠肽 (BNP) 的表达, 减轻心肌细胞凋亡, 减小心脏梗死面积, 并改善心功[123]。

最新研究发现, circRNAs不仅可以抑制miRNAs的功能, 还能与miRNAs结合促进其功能。miR-455-3p是来源于BMP2诱导激酶基因circRNA (circ_BMP2K) 的直接靶点, 但circ_BMP2K并未抑制miR-455-3p的表达和功能, 在TGF-β1和Ang II处理的CFs中circ_BMP2K和miR-455-3p表达均降低, miR-455-3p与

Table 3 circRNAs with implication in cardiac fibrosis. ACTG: Gamma-actin; BMP2K: BMP-2 inducible kinase; CDR1as: Cerebellar degeneration-related protein 1 antisense; Fndc3b: Fibronectin type III domain-containing protein 3B; HIPK3: Homeodomain-interacting protein kinase 3; LAS1L: LAS1-like; NFIB: Nuclear factor I B; PAN3: Poly(A)-nuclease 3; POSTN: Periostin; PsAF: Persistent AF; TMP4: Tropomyosin-4; Ube3a: Ubiquitin protein ligase E3A; Yap: Yes-associated protein

circRNA	Stimulation	Target gene	Pro-/anti-fibrotic	Reference
BMP2K	TGF-*β*1/Ang II	miR-455	Anti	[124]
CDR1as	AMI	miR-7	Anti	[128]
Fndc3b	MI	FUS	Anti	[125]
LAS1L	AMI	miR-125b	Anti	[129]
Yap	TAC	TMP4, ACTG	Anti	[126]
0004104	PsAF	miR-328, miR-30d	Anti	[130]
HIPK3	Ang II, STZ, hypoxia, MI	miR-29b, miR-29b-3p, miR-152-2p, miR-29a	Pro	[120-122,127]
NFIB	MI	miR-433	Pro	[131]
PAN3	MI	miR-221	Pro	[132]
POSTN	MI	miR-96-5p	Pro	[123]
Ube3a	AMI	miR-138	Pro	[133]
010567	Diabetic *db*/*db* mice	miR-141	Pro	[134]
000203	Ang II	miR-26b	Pro	[135]

circ_BMP2K直接结合并促进彼此的表达, circ_BMP2K增强miR-455-3p对靶基因小泛素样修饰蛋白1 (SUMO1)的抑制作用, 从而发挥抗CFs活化、增殖和迁移的作用[124]。

3.2.2 circRNAs与蛋白相互作用调控心肌纤维化

circRNAs还可与蛋白结合调控心肌纤维化的发生和发展。Garikipati等[125]筛选小鼠MI后差异表达的circRNAs发现circFndc3b (III型纤维连接蛋白结构域蛋白3B)表达显著降低, 且同源的人circFndc3b在缺血性心肌病患者心脏组织中的表达也明显下调。过表达心脏内皮细胞中的circFndc3b可以增加血管内皮生长因子-A (VEGF-A)的表达和血管生成活性, 并减少心肌细胞和内皮细胞凋亡, 但突变circFndc3b上miRNAs的全部结合位点后发现circFndc3b的功能并未改变, 说明circFndc3b并非通过miRNAs途径调控心肌纤维化, 而是与FUS结合, 通过FUS/VEGF信号通路减少心肌细胞凋亡和心肌纤维化、减小梗死面积并改善心脏功能。circYap在TAC诱导的小鼠心肌肥厚模型中表达显著减少, circYap与原肌球蛋白4 (TMP4)和*γ*肌动蛋白(ACTG)直接结合形成复合物, 过表达circYap促进TMP4和ACTG的相互作用, 增强TMP4对肌动蛋白聚合的抑制作用, 发挥抗心肌纤维化和心脏保护作用[126]。

3.3 外泌体circRNAs调控心肌纤维化

外泌体circHIPK3对MI诱导的心肌纤维化也具有调控作用。来源于缺氧诱导的心肌细胞中的外泌体circHIPK3通过抑制miR-29a而上调VEGFA的表达, 加速心脏内皮细胞周期进程、增殖和心脏内皮细胞迁移, 促进血管生成, 减小MI面积, 减轻心肌纤维化[127]。

circRNAs调控心肌纤维化的研究目前仍处于初步阶段, 报道较少 (表3)[120-135], 而circRNAs具有良好的稳定性, 功能和作用机制复杂, 有广阔的研究空间。

4 小结和展望

近年来, ncRNAs作为新的调控因子吸引了研究者的关注, 研究发现ncRNAs与心肌纤维化的发生和发展关系密切, ncRNAs通过与RNA、DNA和蛋白结合调控心肌纤维化相关信号通路, 可作为心肌纤维化的潜在治疗靶点, ncRNAs在血浆和组织中的差异表达使其成为心肌纤维化的预警及预后评价标记物, 为心肌纤维化的诊断、预后和治疗提供新手段和思路。目前尚无ncRNAs对心肌纤维化的调控进入临床研究, 原因可能为: 首先, ncRNAs广泛分布于细胞、组织和体液中, 且作用广泛, 靶点多, 导致ncRNAs为基础的应用受到靶向性差的限制, 容易导致脱靶效应。其次, 目前的ncRNAs相关的生物信息学和实验研究没有提供对ncRNAs功能和机制的全面了解。最后, RNAs分子稳定性差, 寻找可稳定高效的运输载体是未来研究的任务和方向。随着科研的不断深入, 将加深对ncRNAs功能的认识; 新型生物材料的研发以及对ncRNAs功能片段的研究可帮助实现ncRNAs相关的靶向治疗。未来ncRNAs的应用将给临床相关疾病治疗带来广阔的前景。

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