

· 综述 ·

lncRNA-miRNA-mRNA轴与心血管疾病发病相关性的研究进展

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[摘要] 长链非编码RNA(long noncoding RNA, lncRNA)是从哺乳动物基因组中转录出来缺乏蛋白质编码潜力的核酸分子,主要从表观遗传学、转录调控和转录后调控3个方面实现基因表达调控,或者直接参与调节蛋白质活性。随着测序技术的进展,发现lncRNA可以充当微小RNA(miRNA)的竞争性内源RNA,再进一步调节mRNA的表达。目前研究证实lncRNA-miRNA-mRNA轴与心血管疾病的发病机制密切相关,文章介绍该轴在心血管疾病发病中的最新进展。

[关键词] 心血管疾病;lncRNA;miRNA;mRNA

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Research progress on the correlation between lncRNA - miRNA - mRNA axis and pathogenesis of cardiovascular disease

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[Abstract] Long non-coding RNA (lncRNA) is a kind of nucleic acid molecule which is transcribed from the mammalian genome and lacks protein-coding potential, it mainly realizes the regulation of gene expression from three aspects of epigenetics, transcriptional regulation and post-transcriptional regulation, or directly participates in regulating protein activity. With the development of sequencing technology, it has been found that lncRNA can be used as miRNA sponge to further regulate mRNA expression, and the lncRNA-miRNA-mRNA axis plays an important role in the pathogenesis of diseases. Current researches confirm that the lncRNA-miRNA-mRNA axis is closely related to the pathogenesis of cardiovascular diseases. In this review, we summarize the latest developments in the known roles of this axis in the pathogenesis of cardiovascular diseases.

[Key words] cardiovascular disease;lncRNA;miRNA;mRNA

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由于不健康的生活方式和人口老龄化的进一步加重,心血管疾病(cardiovascular disease, CVD)的发病率逐年提升^[1],治疗CVD已成为现代医学领域的热点问题。虽然随着新型药物的临床应用和医学科技水平的不断提高,CVD的治疗已经取得很大进展,但仍是最常见的死因,给患者带来了沉重的健康和经济压力^[2]。因此有必要寻求其潜在的分子机制以探索更有效的预防和治疗措施。

全转录组分析发现RNA聚合酶II(RNA-pol II)

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转录而来的非编码RNA(non-coding RNA, ncRNA)比蛋白质编码的mRNA更多,并且与疾病相关的单核苷酸多态性和突变在ncRNA基因座附近显著富集^[3]。另有研究发现ncRNA广泛参与基因调控网络^[4],表明可以从ncRNA角度研究疾病的发生、进展等。

1 非编码RNA治疗心血管疾病的作用机制

非编码RNA是指不编码蛋白质的RNA。它们主要分为小分子ncRNA和较长的ncRNA,前一组包括microRNA、小干扰RNA、核内小分子RNA、piwi相互作用RNA和转运RNA等,后一组包括核糖体

RNA、天然反义转录本和长链非编码 RNA^[5]。

长链非编码RNA(long non-coding RNA, lncRNA)是最广泛的 ncRNA 亚群,涉及多种 CVD 危险因素,包括病理性肥大、血管疾病、血脂异常和代谢综合征等^[6]。lncRNA 是长度大于 200 个核苷酸的 ncRNA,其作用机制与亚细胞定位有关。定位于细胞质的 lncRNA 主要影响 mRNA 的稳定性^[7],调节翻译潜能^[8],或者作为竞争性内源 RNA(competing endogenous RNA, ceRNA)^[9]等发挥作用。而定位于细胞核的 lncRNA 则主要通过调节染色质发挥作用,包括染色质的结构^[10]、重塑^[11]等,或与 DNA 相互作用形成 RNA-DNA 复合物以重编程基因表达^[12],充当分子支架,激活或抑制转录^[13]。

微小 RNA(microRNA, miRNA)是最具代表性的小分子非编码 RNA 类,主要引发基因表达的转录后调节。miRNA 长约 22 个核苷酸,其主要作用是通过结合和沉默特定的目标 mRNA 来抑制蛋白质的表达,从而降低蛋白质的合成^[14]。鉴于 miRNA 与多种心血管疾病相关,如心肌肥厚、心律失常、高血压等^[15],因此可以将 miRNA 和 lncRNA 结合起来讨论其在 CVD 中的作用机制。

此外,目前多种研究表明 lncRNA 可以与 miRNA 相互作用。lncRNA 在转录过程中类似于 mRNA,并具有结构相似性。因此,除靶向 mRNA 以外,RNA 诱导的沉默复合物中的 miRNA 还可靶向调节 lncRNA,并通过不完美的碱基配对降低其结构和功能稳定性^[16]。有趣的是,miRNA 也可以通过某些机制增强 lncRNA 表达。研究表明成熟的细胞质 miRNA 可以进入细胞核并调节 mRNA 和 ncRNA 的核转录^[17]。而“microRNA sponges”机制^[18]以及随后提出的伪靶假说、稀释效应和天然 miRNA 海绵等理论被总结成的 ceRNA 假说^[9]表明,带有 miRNA 反应元件的天然 ceRNA 在细胞内可以通过与靶 miRNA 结合而竞争阻断其功能。作为细胞内最重要的 ceRNA 之一,lncRNA 可能参与 lncRNA-miRNA-mRNA 途径^[19]。在 ceRNA 网络中,lncRNA 可以通过自身的 miRNA 反应元件吸附目标 miRNA,并抑制由 miRNA 介导的靶向 mRNA 降解,这也是 lncRNA 参与的常见转录后调控机制之一^[20]。

2 各种心血管疾病中的 lncRNA-miRNA-mRNA 轴

2.1 动脉粥样硬化(atherosclerosis, AS)

动脉粥样硬化是世界范围内 CVD 死亡的主要原因^[21],其发展是一个复杂的病理化过程,最初由

内皮细胞激活促进,随后炎症细胞募集、平滑肌细胞增殖^[22-23]。新出现的证据表明,lncRNA、miRNA 在血管疾病中发挥重要作用^[24-25]。动脉内膜中的氧化低密度脂蛋白(oxidation low lipoprotein, ox-LDL)通过介导内皮功能障碍或激活内皮细胞,促进 AS 的发展^[26]。人冠状动脉内皮细胞在 ox-LDL 刺激后, Malat1 表达升高,并可通过影响 miR-155 抑制炎症细胞因子的释放,从而增加细胞信号转导抑制因子 1(SOSC1)水平,抑制 JAK-STAT 通路,抑制 AS^[27]。血管平滑肌细胞是 AS 发展的关键因素^[28]。人主动脉平滑肌细胞(HASMC)经 ox-LDL 刺激后, TNK2-AS1 表达上调,并可以作为 miR-150-5p 的 ceRNA 调节血管内皮生长因子 A(VEGFA)和成纤维细胞生长因子 1(FGF1)的表达促进细胞的增殖和迁移,促进 AS 斑块的形成^[29]。HASMC 在经血小板衍生生长因子刺激后, SNHG16 表达上调,通过生物信息学分析和荧光素酶报告基因测定证实 SNHG16 通过作为 miR-205 的 ceRNA 调节 Smad2 表达也可促进 HASMC 增殖和迁移^[30]。巨噬细胞衍生而来的泡沫细胞可形成最早的粥样硬化病变中的脂质条纹,在 ox-LDL 刺激人巨噬细胞后, UCA1 靶向 miR-206 加重氧化应激和凋亡,促进 AS^[31]。平行于血管腔表面的层流切应力在调节抗炎、抗粘连和抗 AS 中起关键作用,从而影响 AS 的发展。人脐静脉内皮细胞经过层流切应力处理后, AF131217.1 表达升高,随后靶向 miR-128-3p/KLF4 轴通过抑制内皮细胞炎症,在 AS 的发病机制中起抗 AS 的作用^[32]。由此可知, lncRNA-miRNA-mRNA 轴与 AS 息息相关(表 1)。

2.2 心肌梗死(myocardial infarction, MI)

由急性冠状动脉阻塞引起的急性心肌梗死是 CVD 患者死亡的主要原因之一,每年疾病影响范围超过 700 万人^[33]。ceRNA 是 lncRNA 调节 CVD 进展的新形式,该功能已被广泛报道用于调节心脏重塑、血管平滑肌和内皮细胞的行为^[34]。MI 的主要原因是血液供应的长期中断,导致心脏某些部位缺乏营养和氧气,最终导致死亡^[33]。研究发现缺氧损伤的 H9c2 细胞中 ANRIL 表达显著增强,沉默 ANRIL 可加重缺氧诱导的损伤,并通过调节 miR-7-5p 增加 SIRT1 表达,在缺氧损伤的 H9c2 细胞中发挥心脏保护作用,为治疗 MI 提供新思路^[35]。缺血-再灌注损伤(I/R)是 MI 患者心脏保护的关键治疗靶点^[36]。I/R 发病机制主要集中在氧自由基、钙超载、炎症反应、线粒体损伤、细胞死亡、内皮细胞损伤和自噬^[37-38]。而自噬是衰老、炎症、肿瘤代谢和心血管疾病的重要过程^[39],在

表1 心血管疾病中的lncRNA-miRNA-mRNA轴
Table 1 lncRNA-miRNA-mRNA axes in cardiovascular diseases

疾病	lncRNA	miRNA	mRNA	作用机制	参考文献	
动脉粥样硬化	Malat1	miR-155	SOSC1	炎症(-)凋亡(-)	[27]	
	TNK2-AS1	miR-150-5p	VEGFA	增殖(+)	[29]	
			FGF1	迁移(+)		
	SNHG16	miR-205	Smad2	增殖(+),迁移(+)	[30]	
	UCA1	miR-206	—	氧化应激(+),凋亡(+)	[31]	
心肌梗死	AF131217.1	miR-128-3p	KLF4	炎症(-)	[32]	
	ANRIL	miR-7-5p	SIRT1	氧化应激(-),凋亡(-)	[35]	
	2810403D21Rik/Mirf	MiR26a	Usp15	自噬(-)	[41]	
			ATG7	自噬(+)	[43]	
	AK139128	miR-499	FOXO4	自噬(+),凋亡(+)	[44]	
	GAS5	miR-525-5p	CALM2	凋亡(+)	[45]	
	心脏肥大	CHRF	miR-489	Myd88	肥大(+)	[15]
		HOTAIR	miR-19	PTEN	肥大(-)	[46]
MAGI1-IT1		miR-302e	DKK1	肥大(-)	[47]	
MIAT		miR-93	TLR4	肥大(+)	[48]	
糖尿病性心肌病	CYTOR	miR-155	IKKi	肥大(-)	[49]	
	DCRF	miR-551b-5p	PCDH17	自噬(+)	[52]	
	MIAT	miR-22-3p	DAPK2	凋亡(+)	[53]	
心房颤动	MEG3	miR-145	PDCD4	凋亡(-)	[55]	
	KCNQ10T1	miR-384	CACNA1C	房颤(+)	[58]	
	TCONS 00075467	miR-328	CACNA1C	心房电重构	[59]	
钙化性主动脉瓣疾病	PVT1	miR-128-3p	Sp1	纤维化(+)	[61]	
	TUG1	miR-204-5p	Runx2	细胞分化(+)	[65]	
	MALAT1	miR-204	Smad4	细胞分化(+)	[66]	
	AFAP1-AS1	miR-155	SMAD5	细胞分化(+)	[67]	

心肌细胞中,自噬维持线粒体的更新,有助于满足心脏的能量需求^[40]。研究发现,2810403D21Rik/Mirf是一种新型抗自噬性lncRNA,沉默该lncRNA可导致miR26a上调,随后通过靶向Usp15促进心肌细胞的自噬和减轻心脏损伤,改善心脏功能^[41]。然而,自噬在MI中的作用仍然具有争议。根据压力的情况,自噬在MI中可以是保护性的或适应不良的。自噬功能障碍可能导致MI后心肌I/R和心室重构,甚至可能引发细胞凋亡和坏死^[42]。如APF是一种自噬促进因子,当APF表达下降时,可通过作为miR-188-3p的ceRNA调节ATG7从而抑制自噬和MI^[43]。同样,AK139128也是一种自噬促进因子,其表达显著上调时,通过负调节miR-499/FOXO4轴促进自噬和心肌细胞凋亡^[44]。心肌细胞凋亡是扩大梗死范围的另一个重要因素,梗死早期和晚期均存在凋亡现象。GAS5在MI后表达上调,沉默GAS5可通过靶向miR-525-5p/CALM2轴抑制心肌细胞凋亡,并改善梗死后心肌细胞的活力^[45]。综上,可以

发现lncRNA-miRNA-mRNA轴为MI的治疗提供了新的治疗靶点(表1)。

2.3 心脏肥大(cardiac hypertrophy, CH)

心脏肥大是心脏对压力/容量超负荷的适应性反应,以在早期维持心脏功能。然而,持续性的CH通常会引发适应不良的心脏重塑,从而导致依从性降低、心力衰竭和猝死的风险增加。因此必须寻找有效的治疗手段,以抑制适应不良的肥大和随之而来的心力衰竭。研究常用主动脉缩窄术(transverse aortic constriction, TAC)建立的小鼠心脏肥厚模型和血管紧张素II或去氧肾上腺素诱导的细胞肥大模型进行实验。在肥厚模型中首次验证的lncRNA为CHRF,其可以靶向miR-489,并进一步调节Myd88的表达水平,从而激活肥大反应^[15]。接下来在TAC动物模型和诱导的细胞肥大模型中验证了多种lncRNA可以通过ceRNA机制调节靶基因从而影响CH。如HOTAIR通过miR-19/PTEN轴在CH中发挥负调节因子的功能^[46],MAGI1-IT1通过靶向miR-

302e/DKK1轴使Wnt/ β -连环蛋白途径失活而在CH中起负调节剂的作用^[47]。MIAT通过在心肌细胞中作为miR-93的海绵而正调节TLR4的表达,在CH中起正向调节作用^[48]。用主动脉缩窄法诱导肾血管高血压建立的肥厚模型中,发现CYTOR可能通过miR-155和下游IKKi和NF- κ B信号转导在CH中起保护作用,最可能通过作为miR-155的ceRNA来抵消miR-155介导的IKBKE抑制^[49]。由此表明,该轴也可参与CH的发生机制,从而作为肥大的治疗靶点。

2.4 糖尿病性心肌病(diabetic cardiomyopathy, DCM)

随着lncRNA-miRNA-mRNA轴在心肌病中的研究进展,人们对DCM的分子机制有了进一步的认识。DCM是心脏病的一种特殊形式,它是由对心脏组织中胰岛素代谢作用的抵抗、代偿性高胰岛素血症和高血糖引起的,而这种疾病的发生独立于其他心脏危险因素^[50],并且越来越多的研究表明氧化应激、炎症、线粒体功能障碍、肾素-血管紧张素系统激活、心肌细胞凋亡都参与了DCM的发病机制^[51]。通过在腹膜内注射链脲佐菌素诱导DCM小鼠模型,并在该模型中发现了几条lncRNA-miRNA-mRNA轴。DCRF可以作为miR-551b-5p的ceRNA增加PCDH17的表达,从而增加心肌细胞自噬,促进DCM的进展^[52]。MIAT可以通过作为miR-22-3p的ceRNA上调DAPK2表达,从而导致心肌细胞凋亡,参与DCM的进展^[53]。MEG3已被证明可参与多种心血管疾病的发展^[54],在DCM中,MEG3在高糖处理的AC16细胞中可作为抑制miR-145表达的ceRNA,减少miR-145对PDCD4的抑制作用,从而减轻AC16细胞凋亡^[55](表1)。

2.5 心房颤动(atrial fibrillation, AF)

心房颤动是目前临床上难以攻克的心律失常,会增加心力衰竭和缺血性卒中的风险,也是造成人群发病率和死亡率高的原因之一^[56]。已知CACNA1C是房颤发展过程中的关键生物标志物^[57],YY1诱导的KCNQ1OT1上调可通过调节miR-384/CACNA1C轴增加血管紧张素II诱导的心房颤动^[58]。电重构在AF的发生和维持中起关键作用,TCNS00075467可通过作为miR-328的ceRNA改变CACNA1C的表达从而调节心房电重构影响房颤^[59]。心房纤维化是AF中心房结构重构的标志,已成为房颤的重要病理生理因素^[60]。PVT1可以充当miR-128-3p的海绵并消除miR-128-3p对Sp1的抑制作用,进而激活TGF- β 1/Smad通路,促进成纤维细胞增殖,胶原

产生和小鼠心房纤维化^[61],而研究表明,TGF- β 1通过Smad蛋白产生促纤维化作用,可以增强心房纤维化和AF^[62](表1)。由此可知,lncRNA-miRNA-mRNA轴可参与AF的发病机制,有助于找到AF的新治疗靶点。

2.6 钙化性主动脉瓣疾病(calcified aortic valve disease, CAVD)

CAVD在成人中具有较高的发病率和死亡率,并且目前没有有效的医学手段来预防或减缓疾病过程^[63]。其瓣叶钙化的主要原因是主动脉瓣叶中静息的瓣膜间质细胞(valve interstitial cell, VIC)被激活并经历表型转变成为成骨细胞样细胞^[64],因此可以通过抑制成骨细胞分化以防止VIC的转化,从而阻止甚至逆转CAVD的进展。研究发现,TUG1可以通过海绵状miR-204-5p调节Runx2的表达^[65],MALAT1可以通过靶向miR-204调节Smad4的表达^[66],AFAP1-AS1也可以通过调节miR-155/SMAD5轴^[67]促进VIC的成骨分化,从而促进CAVD的形成(表1),表明lncRNA在CAVD中可作为新治疗靶点的潜力。

3 lncRNA-miRNA-mRNA轴在心血管疾病的病理生理学中的作用

应激、细胞凋亡、自噬、坏死、纤维化以及心肌细胞、内皮细胞、心脏成纤维细胞和血管平滑肌细胞的增殖和迁移都有助于CVD的发生发展,而上述研究证明该轴在这些CVD的进展机制中起重要作用。如TNK2-AS1可通过靶向miR-150-5p调节VEGFA和FGF1的表达从而调节血管平滑肌细胞的增殖和迁移^[29],GAS5可通过靶向miR-525-5p/CALM2轴调节心肌细胞的凋亡和增殖能力^[45],PVT1可以作为miR-128-3p的ceRNA消除其对Sp1的抑制作用,进而激活TGF- β 1/Smad通路,促进成纤维细胞增殖和小鼠心房纤维化^[61]。

4 结论和展望

近年来,随着ncRNA在多种疾病发展过程中表现出独特的功能,对于lncRNA在心血管疾病发病机制中的认识也进一步加深。本文总结了一些lncRNA-miRNA-mRNA轴在CVD中的作用机制。lncRNA可以通过ceRNA机制正向或负向调节疾病的进展,以作为疾病的新型治疗靶点。并且同一种lncRNA可以靶向不同的miRNA,同一种miRNA也可以被不同的lncRNA靶控,再通过不同的信号途

径发挥效应。但目前大部分实验只局限于动物和细胞,尚未运用到临床,需要进行大规模的临床研究,以观察 lncRNA-miRNA-mRNA 轴的调节能否做为药物治疗的靶点或作为疾病进展的标志物,最终将 ncRNA 运用于临床实践。

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