

肌源性microRNA-133的研究进展

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摘要: MicroRNA-133属内源性非编码microRNA家族成员之一, 主要在骨骼肌和心肌中表达, 因此也被称为肌源性miRNA(myomiR)。肌源性miR-133通过其丰富的生物学功能在多种疾病调控过程中发挥重要的病理生理作用。运动通过调节骨骼肌来源的miR-133表达, 可能是运动防治慢性疾病的重要机制之一。本文将根据国内外研究进展对肌源性miR-133的生物学功能、病理生理意义及运动对miR-133的调节作用等进行综述。

关键词: 肌源性miR-133; 生物学功能; 病理生理作用; 运动

Research progress in myogenic microRNA-133

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Abstract: MicroRNA-133 is a member of endogenous non coding miRNA family, which is mainly expressed in skeletal muscle and myocardium, also known as myogenic miRNA (myomiR). Myogenic miR-133 is closely related to the occurrence and development of many diseases through its rich biological functions. Exercise can regulate the expression of skeletal muscle derived miR-133 to promote the crosstalk between skeletal muscle and other tissues, which may be one of the essential mechanisms for exercise prevents chronic diseases. In this review, we will reveal the biological function, pathophysiological significance of myogenic miR-133 and the regulation of exercise on miR-133 according to the research progress.

Key Words: myogenic miR-133; biological function; pathophysiological effects; exercise

MicroRNA(miRNA)是1993年首次发现的内源性非编码RNA^[1], 成熟的microRNA由18~25个核苷酸构成, 通过碱基互补配对的方式结合靶mRNA, 诱导靶mRNA的降解或阻止其翻译, 在细胞的各个生命活动环节发挥重要调控作用。目前发现数千种microRNA在机体中的表达有明显的组织特异性。MiR-133是2006年由Chen等^[2]在Nature上首次报道发现的, 并证实其在成年人心肌和骨骼肌组织中特异性高表达, 被称为肌源性miRNA

(myomiR)。骨骼肌表达的miR-133不仅作用于骨骼肌自身的蛋白调控, 还可分泌进入血液循环, 或由外泌体包裹进入血液循环, 到达外周的组织器官, 介导骨骼肌与外周组织的交互作用。近年来研究发现, miR-133在肌细胞的增殖分化、细胞凋亡, 血管生成、脂肪组织褐色化等生物学过程中发挥重要的生物学作用, 广泛参与多种疾病的病理生理过程。本文将对miR-133的生物学功能、病理生理意义的研究进展进行综述。

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1 MiR-133的生物学特征及组织分布

在人类基因组, miR-133基因包括*miR-133a-1*、*miR-133a-2*和*miR-133b*, 它们分别位于第18、20和6号染色体上^[3]。MiR-133a-1和miR-133a-2序列相同, miR-133b与miR-133a在3'端呈现出单个碱基的差异, 如图1所示。MiR-133的序列在不同种属间高度保守。MiR-133主要表达于心肌和骨骼肌, 但两种亚型又有区别, 其中miR-133a在骨骼肌和心肌中均有表达, 而miR-133b则主要在骨骼肌表达。与骨骼肌来自同一间充质细胞系的褐色脂肪细胞也有miR-133的少量表达^[4]。此外, 在多种肿瘤细胞中, 如胃癌细胞、乳腺癌细胞、胰腺癌细胞、大肠癌细胞等, 也发现了miR-133的表达。

2 MiR-133的基因表达调控

骨骼肌的分化状态对miR-133的表达有直接的调节作用。MiRNA阵列分析与Northern印迹实验均发现, 在分化培养基培养的第3天和第5天, C2C12肌管细胞中miR-133a/b的表达逐渐增加。胚胎期小鼠未检出miR-133的表达, 新生小鼠的心肌和骨骼肌有少量miR-133表达, 成年小鼠心肌和骨骼肌miR-133表达量显著增加; 人类的研究也有同样的发现, 成熟的骨骼肌miR-133表达丰度最高^[5], 提示miR-133的表达与肌细胞的分化程度密切相关。多种与肌分化相关的转录因子如肌肉分化因子(myogenic differentiation, MyoD)和血清反应因子(serum response factor, SRF)均参与了miR-133的表达调控。MyoD可与miR-133茎环结构的上游片段结合, 显著上调miR-133的表达。有研究报道指出, 多种非编码RNA如circRNA、lncRNA均能与miR-133结合, 调节miR-133在疾病中的表达^[6]。此外, 肥胖、炎症、氧化应激等也对miR-133的表达起调节作用^[7]。

3 MiR-133的生物学功能

与所有miRNA的作用一样, miR-133也是通过与其目标基因结合, 通过转录后调节, 抑制目标基因的表达和蛋白质的翻译来发挥其生物学功能的(图2)。

3.1 调节骨骼肌生成、增殖和分化

肌源性的miR-133对骨骼肌自身有着重要的调节作用。从胚胎干细胞分化开始, miR-133就参与抑制非肌基因的表达, 促进中胚层前体细胞的形成, 在骨骼肌卫星细胞的分化过程中, miR-133通过抑制Prdm16的表达, 促进卫星细胞分化成肌原细胞, 在肌细胞的分化决定中发挥重要作用^[8]。MiR-133还下调SRF的表达, 促进C2C12肌原细胞的增殖; 与Dlh3 3'端非翻译区结合, 促进C2C12细胞的分化^[9]; 与Gli3的3'端非翻译区结合, 促进肌生成^[10]。但也有研究报道, 在C2C12细胞中, miR-133能下调目标基因*IGF-1R*的表达, 抑制PI3K/Akt的激活, 从而抑制肌肉的增殖、分化及肌肉肥大, 参与肌肉萎缩等病理生理过程^[11]。综上, 肌源性miR-133通过下调或抑制非肌基因的表达, 参与调节骨骼肌生长、增殖和分化过程。

3.2 抑制心肌肥大

相较于骨骼肌的研究, 目前miR-133在心肌中的作用受到更多关注。MiR-133通过与多个目标基因作用, 抑制心肌肥大的发生。在 β -肾上腺素受体激动剂或内皮素-1处理诱导的新生和成年小鼠心肌肥大模型中, 外源性给予miR-133能显著抑制肥大相关标志基因的表达, 而抑制miR-133表达后, 则出现明显的心肌肥大。在甲状腺素诱导的心肌肥大模型和糖尿病心肌肥大模型中, 给予外源性的miR-133类似物均显著抑制了心肌肥大的发生^[12]。研究发现, RhoA、Cdc42、Nelf-A/WHSC2和

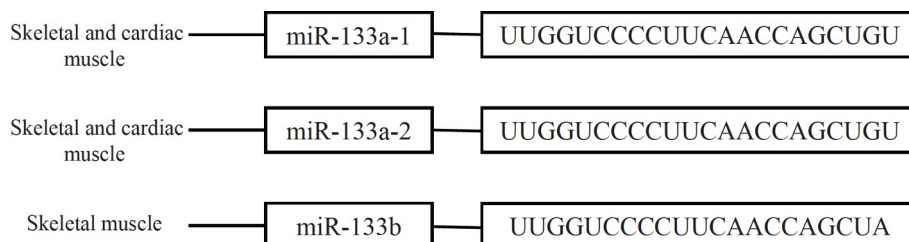


图1 MiR-133家族的碱基序列结构图

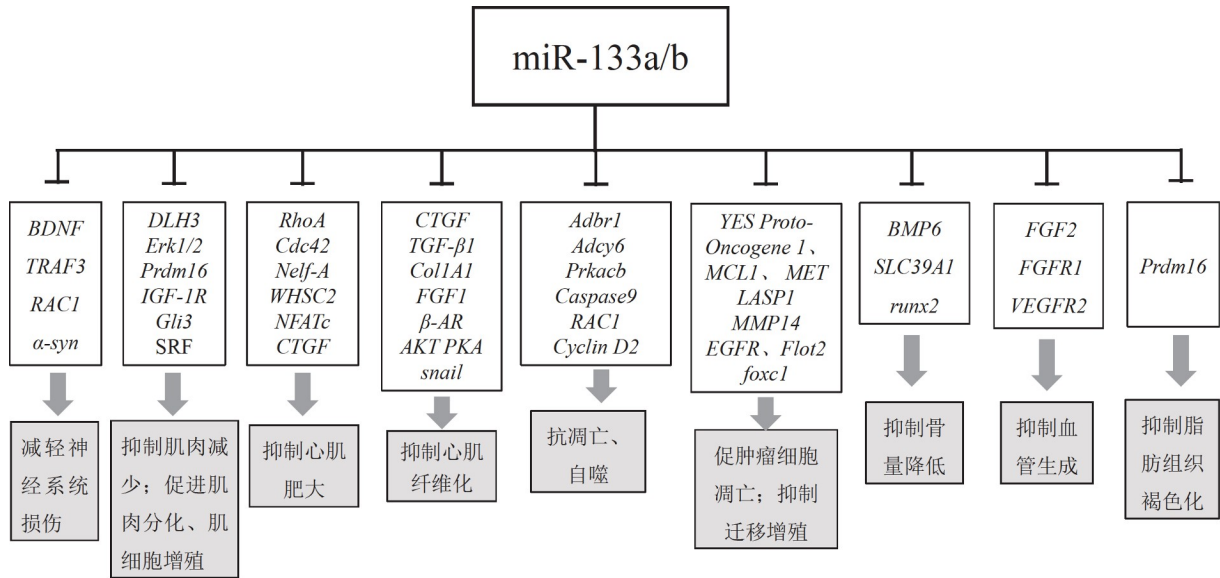


图2 MiR-133的调控靶点及其生物学功能

NFATc4都是miR-133作用的特异性靶蛋白^[13]。综上, miR-133通过抑制上述靶蛋白的表达, 发挥抑制心肌肥大的作用。

3.3 抑制纤维化

MiR-133下调多个诱导心肌纤维化的蛋白因子表达, 抑制纤维化的发生。MiR-133与结缔组织生长因子(connective tissue growth factor, CTGF)的3'端非翻译区结合, 抑制CTGF的蛋白质表达, 逆转心脏基质重塑和膀胱壁重塑时的纤维化改变。*Snail*是上皮细胞间质转型的主要调控者, 是促进纤维化发展的重要因子。MiR-133通过抑制*snail*的表达, 促进心肌纤维细胞向心肌样细胞分化, 抑制心肌纤维化^[14]。此外, miR-133还特异性抑制胶原蛋白1a1(collagen 1a1, Coll1A1)和转化生长因子-β(transforming growth factor-β, TGF-β)的表达, 抑制心肌纤维化, 改善心脏重构^[15]。

3.4 调节细胞凋亡

MiR-133对细胞凋亡的调节作用不尽相同。在正常的组织和细胞中, miR-133抑制凋亡的发生; 而在肿瘤细胞中, miR-133却促进凋亡的发生; 但殊途同归, 均可改善机体健康。在β1肾上腺素受体持续激活诱导的心肌细胞凋亡时, miR-133能显著抑制凋亡的发生, miR-133可以下调60% β1肾上腺素受体(*adbr1*) mRNA的表达, 其受体下游通路中的腺苷酸环化酶6(adenylate cyclase6, AC6)和蛋

白激酶A C-β(catalytic subunit β of cAMP-dependent protein kinase A, PKA C-β, *prkacb*)也均为miR-133的直接靶蛋白, miR-133抑制受体通路的激活, 发挥抗心肌凋亡的作用^[16]。MiR-133还通过抑制Caspase-9的表达, 抑制尼古丁诱导的心肌凋亡^[17]。在大鼠肾上腺嗜铬细胞瘤细胞诱导的帕金森模型中, miR-133作用于其靶蛋白Ras相关的C3肉毒素底物1(ras-related C3 botulinum toxin substrate 1, *RAC1*), 减少凋亡和自噬的发生^[18]。

相反, 在肿瘤细胞中, miR-133有强大的促凋亡效应。表皮生长因子受体(epidermal growth factor receptor, EGFR)是miR-133的直接靶蛋白, miR-133通过抑制EGFR的表达, 促进肿瘤细胞的凋亡, 抑制其增殖和转移, 改善肿瘤的发展^[19-21]。此外, miR-133还能抑制YES原癌基因1的表达, 促进乳腺癌细胞的凋亡^[22]。综上, miR-133通过抑制正常组织细胞凋亡, 同时促进肿瘤细胞凋亡, 对机体健康水平起积极的保护作用。

3.5 抑制血管生成

MiR-133与成纤维细胞生长因子受体1(fibroblast growth factor receptor 1, *FGFR1*)的3'端非翻译区结合, miR-133过表达显著抑制了FGF2/*FGFR1*诱导的内皮细胞的成管和迁移, 干扰毛细血管网的形成, 抑制血管的生成^[23]。生物信息学分析和荧光素酶报告分析均证实, 血管内皮生长

因子受体2也是miR-133的直接靶蛋白, miR-133作用于人脐带血管内皮细胞, 抑制其生存、增殖及迁移活力, 抑制血管的生成^[24]。

3.6 抑制骨生成

MiR-133有抑制成骨细胞分化及促进破骨细胞分化的作用。在骨形成蛋白(bone morphogenetic proteins, BMPs)诱导C2C12细胞成骨样分化时, BMPs通过抑制miR-133的表达, 解除了miR-133对其靶蛋白Runx2的降解作用, 促进成骨分化。此外, miR-133a与靶蛋白SLC39A1结合, 抑制人间充质干细胞的成骨样分化; 在RAW264.7和THP-1c细胞系, miR-133促进它们的破骨样分化, 参与更年期女性骨质疏松的发生^[25,26]。还有研究表明, miR-133a通过作用于靶蛋白基质金属蛋白酶(matrix metallo proteinases, MMPs), 参与细胞外基质纤维化调节, 进而影响骨胶原生成^[27]。

3.7 抑制脂肪组织褐色化

有文章以“关火”来描述miR-133对脂肪褐色化的抑制作用, 提示miR-133在机体能量代谢调节中有重要的意义^[28]。在原代培养的褐色脂肪细胞和基质血管成分细胞中, 抑制miR-133的表达显著促进了脂肪褐色化分化。相反, mimic-miR-133则明显阻断了脂肪褐色化分化^[29]。研究发现, Prdm16是miR-133作用的靶蛋白, 冷应激使皮下白色脂肪组织中miR-133的表达较对照组下调了90%, Prdm16的表达与对照组相比上调约5倍, 表明miR-133在抑制脂肪组织褐色化中发挥了强大效应^[30]。

4 MiR-133的病理生理意义

MiR-133丰富的生物学功能提示其与多种疾病的发生和发展密切相关。多种疾病状态时, miR-133的表达发生显著改变(表1), 并发挥重要的病理生理作用。

4.1 肌病

杜氏肌营养不良症(Duchenne muscular dystrophy, DMD)和贝克肌营养不良症(Becker muscular dystrophies, BMD)是两种严重的进行性肌萎缩遗传疾病。大量临床研究发现, 上述患者血清中多种非编码RNA的水平发生了改变, 其中血清miR-133的表达显著升高^[55]。有研究认为, 血

清中miR-1、miR-133和miR-206的表达水平可以作为DMD的诊断指标^[35]。但肌肉中的miR-133的表达水平与血清中的变化不同, DMD的疾病模型Mdx小鼠肌肉中miR-133的表达显著下降^[56]。肌萎缩侧束硬化症(amyotrophic lateral sclerosis, ALS)患者, 也就是渐冻症患者, 血清中miR-133b的水平显著升高^[57]。在去神经诱导的肌萎缩小鼠中, 快肌纤维为主的胫骨前肌中miR-133b的表达也显著升高。目前多数报道将患者体内miR-133的表达水平作为临床上肌病的诊断指标, 但其在肌病防治中的意义尚不清楚。

4.2 心脏疾病

由多种因素诱导的病理性心脏重构, 心肌中miR-133的表达水平显著降低。肥大性心肌病患者的心房和心室肌miR-133a表达下调。在腹主动脉缩窄^[58]和主动脉弓缩窄诱导的心肌肥大小鼠模型^[41]中, 心肌miR-133的表达显著下调。在血管紧张素Ⅱ^[15]和高血压诱导^[59]的心肌肥大的模型中, 心肌、心脏成纤维细胞中的miR-133表达也显著下降。当心脏重构发展成心力衰竭后, 有临床研究表明, 心肌中miR-133a的表达水平与心衰的严重程度呈反比^[50]。在心肌梗死的患者, 心肌中miR-133a的表达显著降低^[48]。在心肌梗死动物模型中, 心肌中miR-133的表达同样出现显著降低^[47,60]。血液与心肌中的miR-133水平的改变并不一致, 不管是心衰患者^[49], 还是心梗患者^[48], 血清中miR-133的表达均显著升高。大量在体和离体实验提示, 过表达miR-133对心肌细胞有强大的保护作用, miR-133通过抑制心肌细胞凋亡发挥其保护作用^[61-64]。因此, miR-133成为多种治疗心脏疾病药物的作用靶点^[65,66]。

4.3 肿瘤

MiRNA作为翻译后调控的重要方式, 在肿瘤的发病中扮演着重要的角色。MiR-133在多种肿瘤疾病中表达异常, 并通过多条途径参与恶性肿瘤的发生和发展。现有的研究中有近九成的研究表明, 血清或病变组织中miR-133的表达在肿瘤发生时显著降低, 包括消化道肿瘤、肺癌、乳腺癌、白血病、胶质瘤、膀胱癌等^[67-69]。血清miR-133b水平可以作为临床恶性肿瘤病人诊断和预后的标志物^[70]。

表1 MiR-133在疾病时的表达变化

疾病	模型	表达变化	引用文献
神经系统疾病			
急性脑梗死	急性脑梗死患者	血清miR-133水平明显升高	[31]
帕金森病	MPP ⁺ 诱导的帕金森细胞模型	MiR-133a表达明显减少	[18]
	帕金森患者	循环中miR-133b的表达明显下降	[32]
肌病			
慢性阻塞性肺病诱导的肌肉减少症	慢性阻塞性肺病患者	血浆miR-133降低	[33]
杜氏肌营养不良症	杜氏肌营养不良症患者	血清miR-133表达显著升高	[34]
	肌营养不良蛋白缺乏(Mdx)小鼠模型	肌肉中miR-133a表达显著降低	[35]
		肌肉中miR-133b表达降低	
肌肉萎缩	注射肉毒杆菌神经毒素a小鼠	股四头肌注射肉毒杆菌后肌肉miR-133a/b表达降低	[36]
肌萎缩侧索硬化症	肌萎缩侧索硬化症患者	血清miR-133表达增加	[37]
	肌萎缩侧索硬化症小鼠模型	胫骨前肌中miR-133b表达上调, miR-133a表达下调	[38]
肌肉肥大	功能超负荷诱导小鼠跖肌肥大	跖肌pri-miRNA-133a-2转录水平增加约2倍	[39]
心血管疾病			
病理性心肌肥大	甲状腺激素诱导的心肌肥大大鼠模型	心肌miR-133表达降低	[12]
	血管紧张素 II (Ang II)诱导的心肌肥大大鼠模型	心肌miR-133a表达降低	[15]
	横向主动脉缩窄诱导的心肌肥大大鼠模型	心肌miR-133表达降低	[40]
	主动脉弓缩窄诱导的压力超负荷心肌肥大小鼠模型	心肌miR-133表达降低	[41]
生理性心肌肥大	耐力训练诱导大鼠心肌肥大	心肌miR-133的表达显著增加	[42]
心肌病	2型糖尿病或去卵巢诱导心肌病大鼠模型	心脏组织中miR-133表达降低	[43]
心脏细胞凋亡	去卵巢诱导的心脏细胞凋亡大鼠模型	心肌组织Mir-133表达水平降低	[44]
心肌梗死	心肌梗塞患者	心肌miR-133a表达下调	[45]
	冠状动脉结扎小鼠模型	心肌中miR-133表达显著降低	[46]
	冠状动脉结扎大鼠模型	心肌中miR-133表达显著降低	[47]
急性心肌梗死	急性心肌梗死患者	血浆miR-133表达显著升高	[48]
收缩期心力衰竭	收缩期心力衰竭患者	外周血中miR-133-3p的表达水平较高	[49]
冠状动脉疾病	冠状动脉疾病患者	MiR-133a表达降低	[50]
原发性动脉高压	原发性动脉高压患者	血浆miR-133a水平明显低于健康人	[51]
癌症			
结直肠癌	结直肠癌患者	结直肠癌组织中miR-133a-3p、miR-133b-3p表达降低	[52]
三阴性乳腺癌	三阴性乳腺癌患者	MiR-133在乳腺癌组织中显著降低	[22]
急性髓细胞白血病	急性髓细胞白血病患者	患者血清miR-133显著降低	[53]
胃癌	胃癌患者	血清miR-133b水平显著降低	[54]
骨质疏松			
绝经后骨质疏松	去卵巢(OVX)小鼠模型	骨髓间充质干细胞miR-133显著升高	[25]
	绝经后骨质疏松症	血清中miR-133a显著上调	[26]

MiR-133可与多种靶基因结合,通过多种途径发挥其抑癌效应。MiR-133能抑制肠癌细胞的转化和生长^[71],抑制乳腺癌细胞的增殖、促进其凋亡^[22],抑制肺癌细胞的迁移和侵入^[72]。此外,miR-133b与靶基因丙酮酸激酶亚型M2结合,抑制肿瘤细胞中的糖酵解代谢,减少乳酸的生成,改善Warburg效应^[73],抑制肿瘤的发展。

4.4 骨质疏松

绝经后骨质疏松患者血清miR-133a的水平显著升高,骨髓间充质干细胞中miR-133的水平也显著升高^[24]。卵巢切除诱导的雌性骨质疏松大鼠血清miR-133水平显著升高,给予反义miR-133a能阻止大鼠骨质的流失,增加腰椎骨密度^[25]。MiR-133与特异性的靶基因结合,会抑制成骨分化,促进破骨分化,导致骨质疏松的发生。

4.5 神经系统疾病

临床研究发现,帕金森患者血液循环中miR-133b的表达明显下降,并认为miR-133b可以作为帕金森病的生物诊断标志物^[32]。在右侧纹状体鱼藤酮处理诱导的小鼠帕金森模型中,脑部miR-133b的表达显著降低^[74]。MiR-133b与 α -突触核蛋白(α -synuclein, α -syn)的3'非翻译区结合,减轻氧化应激损伤;外源性给予mimic-miR-133b明显减轻了鱼藤酮诱导的神经损伤。在以1-甲基-4-苯基-吡啶离子(1-methyl-4-phenylpyridinium, MPP⁺)处理的肾上腺嗜铬细胞瘤PC-12细胞诱导的帕金森细胞模型中,miR-133a的表达水平显著降低,miR-133a与目标基因*RAC1*结合,减轻了MPP⁺诱导的细胞自噬和凋亡,保护了细胞活性^[18]。临床急性脑梗患者血清miR-133的水平显著升高。有研究提示,miR-133a与脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)结合后,抑制了BDNF的表达,加重了脑的缺血再灌注损伤^[75]。

5 运动对miR-133的调节

运动作为一种非药物干预手段,在多种疾病的防治中发挥了重要作用。骨骼肌作为运动的主要效应器官,其分泌释放的肌源性细胞因子、活性多肽、microRNA及代谢小分子等已被证实参与多种疾病的调控。MiR-133是肌肉组织中特异性表达的miRNA,目前关于运动对miR-133的调节主要

集中于骨骼肌和心肌组织。运动对非肌组织中miR-133的调节尚未见报道。综上,运动诱导肌肉组织分泌释放肌源性miR-133,通过主动转运系统或外泌体携带的方式传递至受体细胞,进而发挥其生物学功能,可能是运动改善健康的关键机制之一。

5.1 有氧运动

血液和肌肉组织中的miR-133的表达受有氧运动调节。一项针对成年男性马拉松运动员的研究显示,耐力运动员血液中的miR-133a表达水平在马拉松比赛后显著增加,有氧运动诱导的循环miR-133a上调与运动员最大摄氧量、心室间隔厚度显著相关,提示可将患者血液循环中miR-133a的表达水平作为有氧能力的生物指标之一^[76]。健康的成年男性在经过7 d中等强度耐力训练后,肌肉活检结果显示急性耐力运动后3 h,骨骼肌miR-133a/b的表达与运动前安静时相比上调35%和40%^[77]。Nielsen等^[78]的研究也证实,骨骼肌miR-133a的表达在60 min有氧运动后明显升高,而经过12周耐力训练后,骨骼肌miR-133a的表达水平在运动前后未发生明显变化。该研究同时指出,健康男性在经过12周的耐力训练后静息时骨骼肌miR-133a/b的表达均明显下调,但在训练结束2周后恢复至训练前水平,提示miR-133可能是运动调控骨骼肌的作用靶点之一。

动物实验发现,8周游泳运动后小鼠心肌miR-133表达明显上升^[79]。如前文所述,miR-133作为心肌的保护因子,在调节心肌肥大方面发挥了重要作用。MiR-133过表达可抑制心肌肥大,反之miR-133表达下降可能与慢性心力衰竭的发生和发展相关。有氧运动通过上调miR-133的表达对心脏起保护作用,可能是运动防治心血管疾病的机制之一。根据已有研究提示,耐力运动调节肌源性miR-133的表达可能与转录因子MyoD、myogenin、PI3K/AKT/mTOR信号通路等作用机制相关^[80,81]。

与健康人群循环miR-133低水平表达不同,病理条件下miR-133呈高表达,有氧运动则有效降低了循环miR-133的表达。Pegoraro等^[82]的研究证实,3~6周的有氧运动使强直性肌营养不良1型患者血清miR-133a/b表达水平明显下降。有关运动调

节miR-133在不同疾病模型中的表达还需更多的研究证实。

5.2 抗阻运动

运动作为生理刺激, 不同的运动形式、运动强度对miR-133的表达产生不同的影响。McCarthy等^[46]对雄性C57BL/6J小鼠进行7 d的功能性超负荷训练, 结果显示, 负荷训练使小鼠腓肠肌和比目鱼肌中pri-miRNA-133a-2的转录水平较开始运动前增加了约2倍, 而miR-133a的表达与开始运动前相比下降了约50%。MiRNA的生成一般是由pri-miRNA经Drosha酶剪切后与Exportin5结合从细胞核运输至细胞质中, 再经Dicer酶切割成为成熟的miRNA。Pri-miRNA与其对应的miRNA表达水平不匹配表明抗阻运动可能对miR-133的形成过程发挥调节作用; 另一方面, miR-133a的表达降低, 减少了对下游靶基因的转录后抑制, 进而促进了骨骼肌肥大, 可能是肌肉对负荷训练的适应机制之一。为验证衰老与骨骼肌特异性miRNA的关系, Drummond等^[83]分别对年轻健康男性(29 ± 2 岁)和老年健康男性(70 ± 2 岁)进行腿部最大力量的抗阻训练, 并在运动结束后进行肌肉活检, 结果表明, pri-miR-133a-1和Pri-miR-133a-2在老年男性中的表达高于年轻男性, 最大强度的抗阻运动后3 h和6 h, 年轻男性股外侧肌中pri-miR-133a-1/2表达出现下降趋势, 反之老年男性在运动后3 h和6 h的pri-miR-133a-1有上升趋势, pri-miR-133a-2在运动后3 h则表达下降, 各组miR-133a在抗阻运动前后均没有显著差异。MiR-133及其前体在老年人群肌肉组织中高表达以及不同人群在抗阻运动不同的反应趋势提示, miR-133可能是运动对抗退行性肌肉萎缩的潜在靶点, miR-133在抗阻训练诱导骨骼肌肥大过程中发挥了调节作用。不同的运动形式及运动剂量效应对不同人群循环或骨骼肌中miR-133表达的影响还有待进一步研究。

6 结语与展望

越来越多的研究发现, 非编码RNA参与了机体基因表达调控过程, 在表观遗传调控、细胞周期调控和细胞分化调控等众多的生命活动中发挥重要作用。但目前对非编码RNA世界的认识还只是冰山一角。肌源性miR-133是目前研究较为充分

的microRNA之一, 其可以与多个目标mRNA结合, 发挥丰富的生物学功能, 广泛参与多种病理生理过程。在今后的研究中, 将miR-133作为临床疾病诊断标志物, 探讨miR-133与其它非编码RNA的相互调节, 了解外泌体介导的miR-133的作用以及miR-133与家族其它成员的协同作用, 研究miR-133在运动改善疾病中的作用及机制都将成为相关领域的热点内容。MiR-133作为肌肉组织特异性的miRNA, 对其进行深入研究将为肌肉组织与外周组织之间的联系方式、交互作用机制探讨提供新思路。

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