·综 述·

运动诱导的 microRNA 与心肌梗死的研究进展

刘向阳, 唐 亮, 吴 健, 欧阳繁, 罗 莘
(中南大学湘雅医学院附属株洲医院 株洲市中心医院心血管内科, 湖南 株洲 412000)

摘要: 运动使心血管系统获益众多, 目前已将运动作为心肌梗死的重要治疗措施之一。由于运动调节心肌梗死(MI)的复杂性, 其具体机制仍未完全阐明。近年来发现运动过程中多种微小 RNAs(microRNAs, miRNAs)的表达发生改变, 并且进一步发现运动诱导的 miRNAs 在 MI 病程中发挥重要作用。因此, 本文重点总结基于运动调控下对于 MI 产生调节作用的 miRNAs 并分析其可能机制, 旨在为运动训练对心肌梗死的临床应用提供更深入的理论依据。

关键词: 运动; 心肌梗死; microRNA; 心血管
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Research progress in exercise-induced microRNAs and myocardial infarction

LIU Xiang-yang, *TANG Liang*, *WU Jian*, *OUYANG Fan*, *LUO Xin*
(Department of Cardiology, Zhuzhou Central Hospital, Xiangya Medical College, Central South University, Zhuzhou 412000, Hunan, China)

Abstract: Exercise brings multiple benefits for cardiovascular system and it has been recommended as one of the therapeutic approaches for myocardial infarction. Owing to the complexity of exercise in regulating myocardial infarction, its specific mechanism has not been fully elucidated. Recently, it has been found that the expressions of a variety of miRNAs have changed during exercise and it has been further found that exercise-induced miRNAs play an important role in the course of myocardial infarction. Therefore, this article focuses on summarizing the regulatory effect of miRNAs on myocardial infarction under exercise regulation and analyzing its possible mechanism, in order to provide a more in-depth theoretical basis for the clinical application of exercise training for myocardial infarction.

Key words: exercise; myocardial infarction; microRNA; cardiovascular

心肌梗死(myocardial infarction, MI)目前仍是威胁人类健康的最严重心血管疾病。MI 所带来的并发症及伴发疾病对患者的预后及生活质量造成严重影响[1]。MI 不仅是由于心肌急性缺血缺氧致使的心肌细胞死亡, 同时伴有缺血周围区心肌细胞凋亡, 过度炎症反应激活, 心肌病理性重塑等[2, 3]。逆转 MI 后病理进程可有效抑制心室重构, 延缓心力衰竭的发生发展并改善预后。

目前认为以有氧运动为核心内容的心脏康复项目是 MI 的重要治疗措施之一[4, 5]。MI 后患者进行运动训练的主要意义在于稳定并逆转病程进展, 控制疾病相关的症状, 减少猝死及再发急性心血管事件风险, 提高患者的预后质量[4]。近年来研究发现运动可调控并诱导多种微小 RNAs(miRNAs)从而起到心脏保护作用[6]。miRNAs 是一类由 18 ~ 22 个核苷

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通讯作者: 罗莘, 教授, 主要从事心血管内科、冠心病的研究 Email: luoxin92@sina.com
作者简介: 刘向阳, 硕士生 Email: 824698198@qq.com

酸组成的短链非编码 RNAs, 主要在转录或转录后水平调节基因表达从而调控一系列病理生理过程[7]。研究发现 miRNAs 对 MI 有广泛调控作用, 包括线粒体生物学功能、调控心肌重塑、血管新生及心肌肥厚等病理过程[6, 8]。因此, 本文重点总结运动诱导的心脏特异性或心脏大量表达的 miRNAs 对 MI 的调控。

1　miR-208 和 miR-499

miR-208 和 miR-499 主要在心脏生长发育晚期起调控心肌成纤维细胞及心肌细胞的分化发育作用, 主要调控心脏的重链肌球蛋白基因的内含子表达并对肌浆网收缩蛋白有决定性调节作用, 对心脏的传导系统及维持正常心功能也有重要作用[9]。miR-208 和 miR-499 是心肌中高表达的 miRNAs, 对 MI 同样有重要预测意义[9]。在急性心肌梗死(AMI)或心肌损伤后, 血浆 miR-208 显著升高, 与肌钙蛋白变化时间一致[10]。而 miR-499 与 AMI 中与肌酸激酶及肌钙蛋白也呈正相关, AMI 时, 血浆 miR-499 升高幅度约 100 到 300 倍[11]。

miR-208 促进 MI 后心肌细胞凋亡。Yan 等[12]在新生乳鼠心肌细胞低氧损伤中发现抑制 miR-208 表达后可减轻心肌细胞损伤。而 Bian 等[13]发现过表达 miR-208 显著加重大鼠缺血再灌注(I/R)损伤并促进体外低氧诱导的心肌细胞凋亡, 而敲除 miR-208 可抑制凋亡, 进一步研究发现 miR-208 通过调控靶基因 Ets1 表达诱导的心肌细胞凋亡。此外, 研究表明, 通过注射 antagomiR 下调 miR-208 表达可有效阻断病理性心肌重构, 预防病理性肌球蛋白转化, 抑制心肌纤维化并改善心功能[14]。miR-208 的表达被发现与 β 肌凝蛋白重链(β- MHC)以及心脏胶原容量呈正比。因此, 抑制 miR-208 表达可能成为 MI 后的重要治疗措施。

miR-499 对 MI 的多个病理过程均有重要调控作用。Wang 等[15]发现 miR-499 可减轻心脏 H_2O_2 诱导的心肌细胞凋亡, 在大鼠心肌细胞中过表达 miR-499 可抑制经线粒体凋亡途径以及促凋亡因子基因表达, 从而增加细胞存活率。促凋亡因子双特异性酪氨酸磷酸化调节激酶 2(dual specificity tyrosine-phosphorylation-regulated kinase 2, Dyrk2)通过促进 P53 的磷酸化促进凋亡, 而 miR-499 可抑制 Dyrk2 保护激活的 P53 转位到线粒体从而与促凋亡因子作用(Bak, Bax, Bid)而诱导凋亡过程。miR-499 也可抑制心肌细胞凋亡通过抑制分裂调节蛋白-1(dynamin-related protein1, Drp-1)去磷酸化进而抑制 Drp1 在线粒体中积聚及线粒体融合[16]。此外, 研究发现, 在缺氧-复氧条件下, miR-499 可通过抑制 Sox6 的表达来减轻 H9C2 细胞的损伤并且通过增加 Bcl-2、降低 Bax 和 caspase-3 的表达来抑制细胞凋亡[17]。因此, miR-499 是重要的调控 MI 后的干预靶点。

作为肌源性 miRNAs, miR-208 和 miR-499 的表达均受运动调控。Soci 等[18]发现高运动量游泳显著抑制 miR-208 表达, 从而维持正常生理状态。Stølen 等[19]发现马拉松运动员在运动后 miR-499 显著升高, 运动后 24 h, miR-499 表达量下降至正常水平。提示运动可调控 miR-208 和 miR-499 的表达。因此, 在 MI 后进行运动训练可能是通过调控 miR-208 和 miR-499 的表达改善 MI 后病理过程。

2　miR-1 和 miR-133

miR-1 和 miR-133 高表达于心肌和骨骼肌, 在心脏生长发育早期有重要生理调控作用, 对心肌自律性、传导性、收缩性及肌细胞分化增殖均有重要作用[9]。MI 后循环中 miR-1 和 miR-133 表达均有改变, 可作为 MI 的重要标志物[20, 21]。AMI 使 miR-1 表达显著升高, 在灵长类动物急性心肌 I/R 损伤时, 循环中 miR-1 升高 200 倍左右[22]。随着研究深入, miR-1 亦被发现在 MI 后左心重塑方面有着重要的预测意义[23]。而 miR-133 的表达与调控不同于 miR-1, MI 患者及大鼠 I/R 模型中均检测到 miR-133 表达显著下调[22]。因此, miR-1 和 miR-133 可作为 MI 的重要生物学指标。

尽管目前对 miR-1 在 MI 后的调控作用尚存在争议, 但大部分研究认为 miR-1 在 MI 后以抗凋亡作用为主。在 miR-1 转基因大鼠的心肌细胞中, miR-1 过表达通过激活 AKT 信号通路, 激活抗氧化应激酶, 从而降低 H_2O_2 诱导氧化应激状态[24, 25]。在大鼠压力负荷性心肌肥厚模型中, 心脏特异性腺病毒过表达 miR-1 可显著减少心肌纤维化及凋亡, 从而增加心功能, 而其具体保护机制与调控纤维蛋白-2(fibullin-2, Fbln-2)相关[26]。Huang 等[27]报道了在 MI 后移植过表达 miR-1 的胚胎间充质干细胞可抑制宿主心肌细胞凋亡、抗氧化应激及纤维化并促进心脏再生。提示 miR-1 对 MI 有重要保护作用, 其对于改善 MI 的其他机制也值得进一步发掘。

在 MI 后, miR-133 主要作用表现为抗凋亡。Li 等[28]发现在体外低氧再灌注模型及大鼠 I/R 损伤模型中, 过表达外源性 miR-133 显著减轻心肌细胞的凋亡, 这与抑制死亡相关蛋白激酶 2(death associated protein kinase 2, DAPK2)表达相关。同时 miR-133

被进一步发现能够通过抑制多种促凋亡基因,例如DAPK2、caspase-9和凋亡蛋白酶激活因子等,从而发挥抑制细胞凋亡作用[29]。此外,Izarra等[30]研究发现miR-133转基因的心脏干细胞较非转染miR-133的心脏干细胞更具有抗凋亡能力并增强心肌细胞的再生能力。在MI大鼠模型中,过表达miR-133可显著促进血管新生及心肌细胞增殖,抑制心肌肥厚及纤维化,从而改善心功能。Lee等[31]进一步发现过表达miR-133可增强人间充质干细胞治疗的活性,MI后大鼠予转染miR-133的充质干细胞干预后可显著增强心肌再生及抗凋亡等作用,而其具体机制与表皮生长因子受体被抑制相关。因此,过表达miR-133对MI后细胞治疗过程中也有重要意义。

miR-1和miR-133受运动调控,但研究结果不一。有研究发现马拉松运动员在运动后miR-1及miR-133表达显著上调[32]。而其他研究认为miR-1和miR-133在运动后表达显著下调[33]。该结果不同可能与选取的研究对象不同及运动时间、运动量不同相关。尽管miR-1和miR-133作为心肌中大量表达的miRNAs对MI后的研究仍有争议,但大部分研究认为其具有保护作用。因此,miR-1和miR-133作为运动可诱导的miRNAs,对MI的病理过程有重要调控作用。

3 miR-126和miR-92a

miR-126和miR-92a主要来源于内皮,对MI后血管新生有重要意义。miR-126和miR-92a与MI密切相关,在MI后二者表达发生改变[34]。但目前MI后miR-126与miR-92a表达变化研究结果不一致,这可能与不同研究中选用不同研究对象及MI后时间不同相关。其表达改变仍可能是MI后的重要预测指标。

miR-126是MI后调控梗死区血管新生的重要miRNA,对AMI后血管新生起促进作用。研究发现,在MI后,心脏中miR-126表达改变明显,并且通过负性调节其靶基因Spred1发挥促血管生成作用来维持血管壁的完整性[35]。而Huang等[36]发现过表达miR-126可上调间充质干细胞中的内皮生长因子、成纤维细胞生长因子-2以及Delta-like 4等基因的表达,促进缺血心肌中血管新生。Chen等[37]进一步发现予转染miR-126的间充质干细胞干预MI后小鼠显著增强MI后缺血区血管新生,从而增强心功能,其具体机制与激活AKT/ERK信号通路相关。此外,近期有研究发现,在MI中,miR-126对于心肌细胞自噬以及凋亡方面同样发挥着调节作用[38]。

miR-92a主要对AMI后血管新生起抑制作用。miR-92a调控的血管新生相关的最重要靶基因是ITGA5和SIRT1[39]。Bellera等[40]发现在AMI大动物模型中,经冠脉给予包含antagomiR-92a微粒干预从而抑制心脏miR-92a表达,可显著促进心肌缺血区血管新生,使受损的心功能明显恢复。而Hinkel等[41]在猪的MI模型中局部使用反义核苷酸沉默miR-92a表达后,显著抑制缺血区心肌细胞凋亡并促进血管新生,缩小MI面积并改善心功能,其作用靶基因同样是ITGA5。因此,抑制miR-92a表达有望成为MI后的重要治疗措施。

miR-126和miR-92a的表达同样受运动调控。miR-126在运动后表达显著上调,并可促进心肌梗后缺血区域血管新生。Uhlemann等[42]发现健康人在最大症状限制性运动测试或者4 h踏车运动后分别可使miR-126表达上调2.1倍以及4.6倍。Wahl等[43]检测不同形式运动对健康受试者miRNAs表达影响,结果发现间歇性冲刺训练后循环中miR-126表达上调2.2倍,而高强度运动训练后miR-126表达上调1.9倍。尽管目前运动对miR-92a表达的研究较少,但已有研究提示运动对miR-92a的表达有调控作用[44]。

4 其他miRNAs

miRNA-21主要在内皮细胞中表达,并被证实其在MI中发挥着重要保护作用。Wang等[45]研究发现miRNA21在AMI的老年患者的血清中表达上升,并进一步发现其能够通过激活JNK/p38/caspase-3信号通路抑制肿瘤坏死因子-α(TNF-α)诱导的人心肌细胞凋亡。有意思的是,在MI后,miRNA21亦可通过促进心脏中成纤维细胞向肌成纤维细胞的转化从而发挥抗纤维化作用,其具体机制与其调节靶基因Jagged1密切相关[46]。miRNA-21已被证实在运动过程中表达上升[43]。

此外,已有研究发现miR-29、miR-146等多种miRNAs在MI后的病程中有重要调控作用,而这些miRNAs的表达同样能受运动调节[8, 43, 47, 48]。因此,随着对miRNAs认识的不断提高,相信更多受运动调控的并在MI病程中发挥重要调节作用的miRNAs会被发掘出来。

5 总结与展望

综上所述,在MI发生后,miR-499、miR-1、miR-133、miR-126与miR-21主要发挥着心脏保护作用,而miR-208和miR-92a导致心肌损害加重,其

中 miR-499、miR-208、miR-1 与 miR-21 在 MI 后表达上升，而 miR-133 表达下降（miR-92a与 miR-126 表达存在争议），并且研究发现运动可以致使 miR-499、miR-126 和 miR-21 表达上升，miR-208 和 miR-92a 表达下降（miR-1 与 miR-133 表达存在争议）。因此，从中我们发现基于运动调控下的 miRNAs 在 MI 的发生发展中发挥着重要调控作用，并且在运动对 MI 后获益的机制中占据重要地位。有意思的是，现阶段也发现运动可诱导骨骼肌、心肌及其他器官来源的多种多肽分子以及相关代谢产物来对 MI 产生调节作用。因此，除了 miRNAs 外，探究运动调节 MI 预后的其他机制可能为运动使 MI 获益中提供新的思路。

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