运动调控miRNA改善非酒精性脂肪性肝病机制的研究进展

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摘要 非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是一类常见的慢性肝病, 包括非酒精性单纯性脂肪肝、非酒精性脂肪性肝炎等, 常并发其他代谢病症, 严重影响人类身体健康。运动锻炼作为预防与治疗NAFLD的一种有效方式, 可以调控相关miRNA表达靶向干预NAFLD病程中的脂质代谢、炎症反应、氧化应激、肝细胞凋亡、肝组织纤维化等。该文梳理前人研究成果, 阐述运动改善NAFLD过程中相关miRNA的作用, 探讨运动、miRNA、NAFLD之间的关系及运动调控miRNA表达改善NAFLD的机制, 以期为运动干预治疗NAFLD机制探究提供参考。

关键词 运动; 非酒精性脂肪性肝病; miRNA

Research Progress on the Mechanism of Exercise Regulating miRNAs to Improve the Non-Alcoholic Fatty Liver Disease

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Abstract NAFLD (non-alcoholic fatty liver disease) is a common type of chronic liver disease, including non-alcoholic simple fatty liver, non-alcoholic steatohepatitis, etc. It is often complicated with other metabolic diseases, which seriously affects human health. As an effective way to prevent and treat NAFLD, exercise can regulate the expression of related miRNAs to target lipid metabolism, inflammation, oxidative stress, hepatocyte apoptosis, and hepatic tissue fibrosis in the course of NAFLD. The article combed through the previous research results and elaborated on the role of relevant miRNAs in the process of improvement of NAFLD by exercise, explored the relationship between exercise, miRNA, NAFLD, and the mechanism of exercise regulating miRNA expression to improve NAFLD, with a view to providing a reference for the exploration of the mechanism of exercise intervention in the treatment of NAFLD.

Keywords exercise; NAFLD; miRNA

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是指除大量酒精摄入外, 因药物、遗传、高脂饮食及其他肝损伤因素造成肝细胞脂质变性与异常沉积的一类肝代谢疾病, 其病理症状主要表现为肝细胞弥散性气泡样脂肪变性与甘油三酯(triacylglycerol, TG)蓄积等。NAFLD疾病谱包括非

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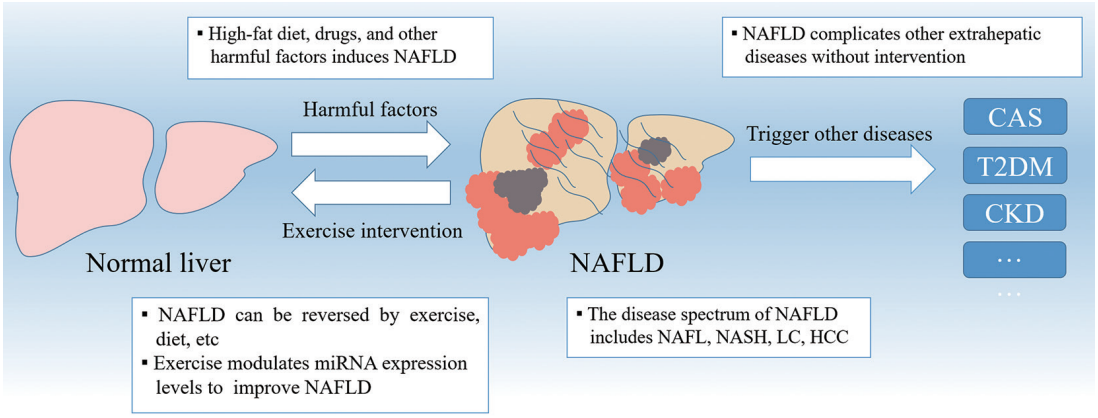


图1 NAFLD的病程发展与逆转(根据参考文献[1]修改)

Fig.1 Development and reversal of NAFLD (modified from the reference [1])

酒精性单纯性脂肪肝(non-alcoholic simple fatty liver, NAFL)、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)、肝硬化(liver cirrhosis, LC)和肝癌(hepatocellular carcinoma, HCC), 常并发冠状动脉粥样硬化(coronary atherosclerosis, CAS)、慢性肾脏病(chronic kidney disease, CKD)、II型糖尿病(type 2 diabetes mellitus, T2DM)等代谢性疾病(图1)。现阶段临床上尚无治疗NAFLD的特效药, 而规律的运动锻炼作为治疗NAFLD的非药物手段之一, 成本低且对患者身心有积极作用[1]。

NAFLD的致病机制涉及多方面, 包括肝脏的脂质代谢、炎症反应、肝细胞凋亡等。最新研究显示, NAFLD的诱发与个体的微小RNA(microRNA, miRNA)表达存在一定关系, 同时已有证据表明运动可以通过调控miRNA表达水平以改善NAFLD[2-3]。近年来, 聚焦于干预miRNA表达治疗NAFLD的报道越来越多, 但对于运动影响miRNA表达治疗NAFLD的研究仍存在一定不足。因此, 本文综述了运动、miRNA、NAFLD三者之间的关系, 及运动干预miRNA表达以改善肝脏脂质代谢、炎症反应、氧化应激、肝细胞凋亡等的机制, 以期为探究运动改善NAFLD的机制和开发新的防治策略提供参考。

1 miRNA与NAFLD

miRNA是一类在真核生物中长度为21~23个核苷酸的非编码调控性单链小分子RNA, 可通过与靶mRNA特异性的碱基配对使之降解或者抑制其翻译, 从而控制基因表达及细胞分化、增殖和凋亡等[4-6]。多数miRNA具有组织特异性表达, 例如miRNA-18、miRNA-20存在于肺脏组织中; miRNA-122、miRNA-192存在于肝脏组织中等[7]。其中, 肝脏特异性miRNA的表达对于NAFLD有着不同的作用: miRNA-21的高表达会促进肝细胞的脂质变性与合成, 抑制miRNA-21的表达可改善NAFLD个体的脂质代谢与肝纤维化[8-9]; miRNA-193a-5p的高表达对NAFLD患者的氧化应激起到改善作用[10]; miRNA-34a表达受抑制可改善NAFLD个体的炎症反应并缓解肝细胞凋亡[11]。

miRNA的表达途径如下: 细胞核内miRNA基因经RNA聚合酶II(RNA polymerase II, RNA Pol II)催化转录生成初始miRNA(primary miRNA, pri-miRNA), pri-miRNA后被核内Drosha RNase剪切为长度约70个核苷酸并具有茎环结构的前体miRNA(precursor miRNA, pre-miRNA), pre-miRNA通过核质/细胞质转运蛋白5(Exportin-5)从细胞核运输到细胞质, 随后通过Dicer裂解成长度为21~23个核苷酸的双链miRNA。成熟的miRNA依据序列互补形成双螺旋链, 随后与诱导RNA基因沉默组件(RNA-induced silencing complex, RISC)相结合形成非对称基因沉默复合物, 随后该复合物结合到目标mRNA上(图2)[12]。需要注意的是, 多数情况下, 复合物中的miRNA链与目标mRNA会不完全相互配对, 以起到阻断基因翻译过程的作用。人类约有50%蛋白编码基因受miRNA调控, 而几乎所有肝脏细胞的生化过程都涉及miRNA调控[13-14], 如miRNA-155表达受抑制的NAFLD小鼠中脂肪分化相关蛋白(adipose differentiation-related protein, *Adrp*)、二酰基甘油酰基转移酶2(diacylglycerol acyltransferase 2, *Dgat2*)、肉碱棕榈酰转移酶1A(carnitine palmitoyl-

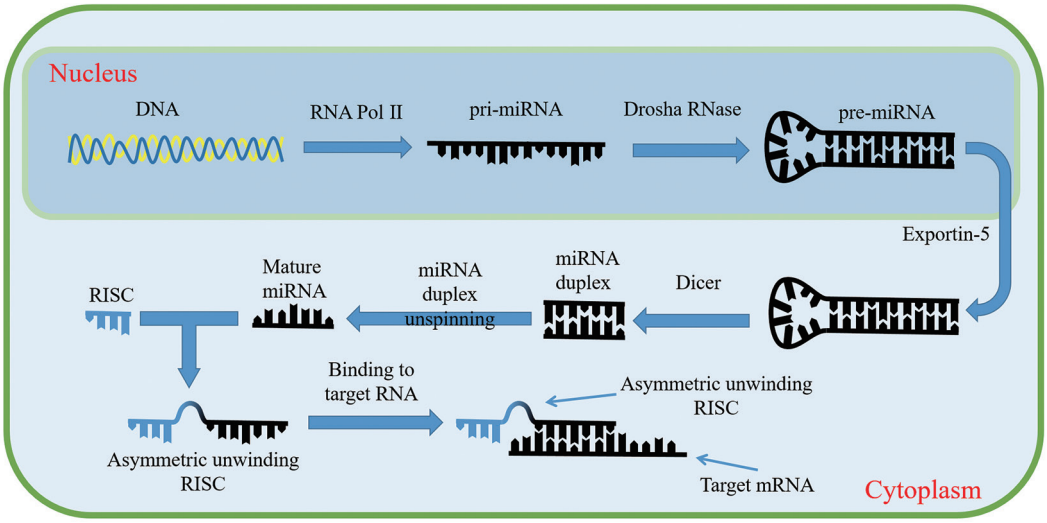


图2　miRNA的生成与表达(根据参考文献[11]修改)

Fig.2　Generation and expression of miRNA (modified from the reference [11])

transferase 1A, *Cpt1a*)等脂质代谢相关基因的表达水平降低, 以减轻脂质沉积与变性[15]。

运动干预对于miRNA基因表达可起到诱导作用, 不同的运动类型、强度、时间等对于miRNA表达产生的影响也不同[16]。目前, 诸多研究表明运动可通过改善线粒体代谢、改变表观遗传等多种途径, 调控与NAFLD病程发展密切相关的肝脏特异性miRNA表达[3,17-18], 以抑制肝组织异常脂质代谢、氧化应激、炎症反应等, 并提升肝细胞抗氧化、抗炎症、抗凋亡与纤维化能力[19-22]。以上研究提示运动可调控相关miRNA的表达以改善NAFLD, 且此过程中脂质代谢、炎症反应、氧化应激、肝细胞异常凋亡、肝纤维化相关的miRNA表达起到重要作用。

2　运动调控miRNA表达改善NAFLD的机制

2.1　运动调控miRNA表达改善NAFLD病程中的脂质代谢

肝脏是人体脂质代谢的重要器官, NAFLD致病与个体的脂质代谢紊乱密切相关。脂质代谢过程受多种生理活动(包括脂质生成、脂肪酸氧化等)影响, 该过程异常会导致TG过度沉积, 使得肝脏脂质沉积、脂肪变性, 并促使肝脏组织产生促炎因子, 诱发线粒体功能障碍与氧化应激等, 导致肝细胞异常凋亡及纤维化, 最终诱发NAFLD[23-24]。通过调控miRNA-122、miRNA-20a-5p等肝脏脂质代谢相关miRNA表达, 改善患者线粒体功能与脂质代谢情况, 对于治疗NAFLD有一定应用前景[25-26]。因此, 运动对于脂质代谢相关miRNA的调控值得重视。

肝脏miRNA-122表达受抑制会导致脂肪酸合成酶(fatty acid synthase, *Fas*)、乙酰辅酶A氢化酶(acetyl CoA carboxylase, *ACC*)等脂质合成相关基因过表达, 而8周以上中等强度的有氧运动可显著上调NAFLD小鼠肝脏miRNA-122表达水平, 靶向抑制甾醇调节元件结合蛋白1(sterol regulatory element binding protein 1, *SREBP1*)(该基因过表达可促使小鼠出现脂质代谢紊乱并诱发炎症)表达, 降低下游脂质合成基因*Fas*、*ACC*及炎症因子白细胞介素-6(interleukin-6, IL-6)、肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)的表达水平, 并改善患病小鼠的肝脏脂质沉积与变性[27-29]。miRNA-192-3p是一种存在于肝脏的类脂质调节因子, 2个月中低强度有氧运动可有效上调肥胖大鼠的miRNA-192-3p表达水平, 阻断肝脏糖皮质激素受体(glucocorticoid receptor, *GCR*)基因表达, 并抑制肝脏脂质合成以预防NAFLD[30-31]。VENUGOPAL等[32]和TORRES等[33]通过细胞实验发现抑制TNF-α可促进miRNA-194表达, 并抑制肝星状细胞(hepatic stellate cell, HSC) Rac GTP酶激活蛋白-1(Rac GTPase activating protein-1, *Rac-1*)及脂质合成靶基因3-羟基-3-甲基戊二酰辅酶A合酶(3-hydroxy-3-methylglutaryl-CoA, *Hmgcs*)、载脂蛋白A5(apolipoprotein A5, *Apoa5*)的表达, SIMAITIS等[34]研究证实3个月中高强度的有氧运动可促使T2DM患者miR-

NA-194的表达水平显著上升, 并改善胰岛素抵抗, 这对于理解运动治疗NAFLD的机制有一定意义。通过药物手段可以抑制NAFLD小鼠miRNA-21表达, 降低下游脂质合成因子*Fas*、*ACC*的水平, 以改善NAFLD的脂质变性与合成情况[8]。6周中等强度有氧运动也能抑制miRNA-21的表达并降低*Fas*、*ACC*的表达水平[35]。与正常人相比, NAFLD患者的miRNA-26a表达水平相对较低, 恢复其表达可减轻内质网应激与脂质沉积[36], miRNA-26a高表达可抑制NAFLD的脂肪变性与炎症反应[37]。PELOZIN等[38]证明10周负重(5%体重)有氧运动可增加小鼠miRNA-26a的表达水平, 同时激活蛋白激酶B/哺乳动物雷帕霉素靶蛋白(protein kinase B/mammalian target of rapamycin, Akt/mTOR)信号通路使小鼠的心室肥大, 这对于改善脂质代谢情况有一定积极意义。核因子E2相关因子2(nuclear factor-erythroid 2-related factor 2, *Nrf2*)是肝脏中改善脂质沉积与氧化应激的重要基因之一, 而HepG2细胞中miRNA-27的过表达会降低*Nrf2*水平, 造成TG水平上升并促进脂质积累[39], 但徐建方等[40]发现4周中低强度低氧运动可有效降低miRNA-27水平, 上调下游靶基因过氧化物酶体增殖物激活受体γ(peroxisome proliferator activated receptor γ, *PPARγ*)(脂代谢转录调控因子基因之一)的表达, 减少大鼠脂质合成、沉积并预防NAFLD(表1)。如前所述, NAFLD的脂质代谢情况与多种miRNA的表达密切相关, 运动调控与肝脏脂质合成、代谢、沉积等相关miRNA的表达, 改变*Fas*、*Nrf2*等下游基因表达水平, 减少脂质合成、抑制脂质沉积与变性并加速代谢, 进而改善NAFLD个体的脂质代谢(图3)。通过运动介导miRNA表达来干预脂质代谢已成为治疗NAFLD的新方式, 运动改善NAFLD患者脂质代谢的过程中, 相关miRNA表达的改变值得更密切的关注。

2.2 运动调控miRNA表达改善NAFLD病程中的炎症反应

在NAFLD病程发展中, 诸多阶段均有炎症反应的出现, 这也是区分NAFL、NASH等疾病的重要病理特征[41]。炎症反应在NAFLD病程中存在利弊两方面: 炎症可以通过促进肝脏再生和清除受损肝细胞来修复肝脏, 但持续的炎症会对正常生理活动产生负面影响, 并破坏组织结构, 导致肝纤维化的发生[42]。miRNA参与肝脏组织炎症反应并影响NAFLD病程发展[43-44], 但其具体影响需要依据miRNA、炎症细胞、炎症因子及所处病程阶段进行综合考虑, ZHU等[45]发现运动对于NAFLD病程中的过度炎症反应具有抑制作用。

miRNA-33过表达有利于改善NAFLD患者的胰岛素抵抗、脂肪变性及炎症反应, 限制NAFL发展为NASH与HCC[46], 李明锐等[47]发现8周中低强度有氧运动会维持小鼠肝脏miRNA-33的高水平, 并抑制三磷酸腺苷结合盒转运蛋白A1(ATP binding cassette transporter A1, *ABCA1*)(一种促脂质合成基因)表达以抑制肥胖与炎症反应。NAFLD患者肝脏中miRNA-34a大量表达, 通过药物抑制miRNA-34a的表达可以改善炎症、肝细胞凋亡及脂质合成情况[11], WANG等[19]研究显示12周低强度有氧运动可上调NAFLD小鼠肝细胞中肝腺苷脱氢酶(adenosine deaminase, ADA)表达, ADA的过表达对于抑制miRNA-34a表达有显著作用, 这提示运动可以改善NAFLD个体由miRNA-34a导致的过度炎症反应, 但miRNA-34a的靶基因尚未明确。miRNA-23b缺失会诱发小鼠NAFLD, 提高miRNA-23b表达水平可减轻NAFLD小鼠炎症反应、肝细胞凋亡与纤维化[48], 研究也显示8周有氧与阻抗联合训练能上调并维持miRNA-23b水平, 并抑制炎症反应, 但其具体机制仍需要深入探讨[20]。肥胖小鼠miRNA-27的表达上调会抑制*PPARγ*表达并激活巨噬细胞, 促进炎症因子TNF-α和IL-6的释放[49-50], 加重炎症反应, 但运动可以有效抑制miRNA-27的表达并上调*PPARγ*, 同时下调下游基因*ABCA1*的表达, 抑制炎症反应[40](表1)。总而言之, NAFLD病程中的过度炎症是病情发展的重要因素, 运动可调控与炎症反应相关的miRNA, 靶向干预如*PPARγ*、*ABCA1*等基因, 抑制炎症因子与脂质合成基因表达, 减轻肝脏组织受持续性炎症的影响, 有利于患病个体的肝脏组织修复, 起到改善NAFLD的目的(图3)。因此, 探究运动通过调控相关miRNA表达以抑制NAFLD病程中的炎症反应, 对于治疗NAFLD有重要意义。但需要注意的是, 部分miRNA受运动调控的机制仍不明确, 需要更全面的研究。

2.3 运动调控miRNA表达改善NAFLD病程中的氧化应激

适量的活性氧(reactive oxygen species, ROS)对于提升细胞适应性有益[51], 但过量ROS会加剧细胞

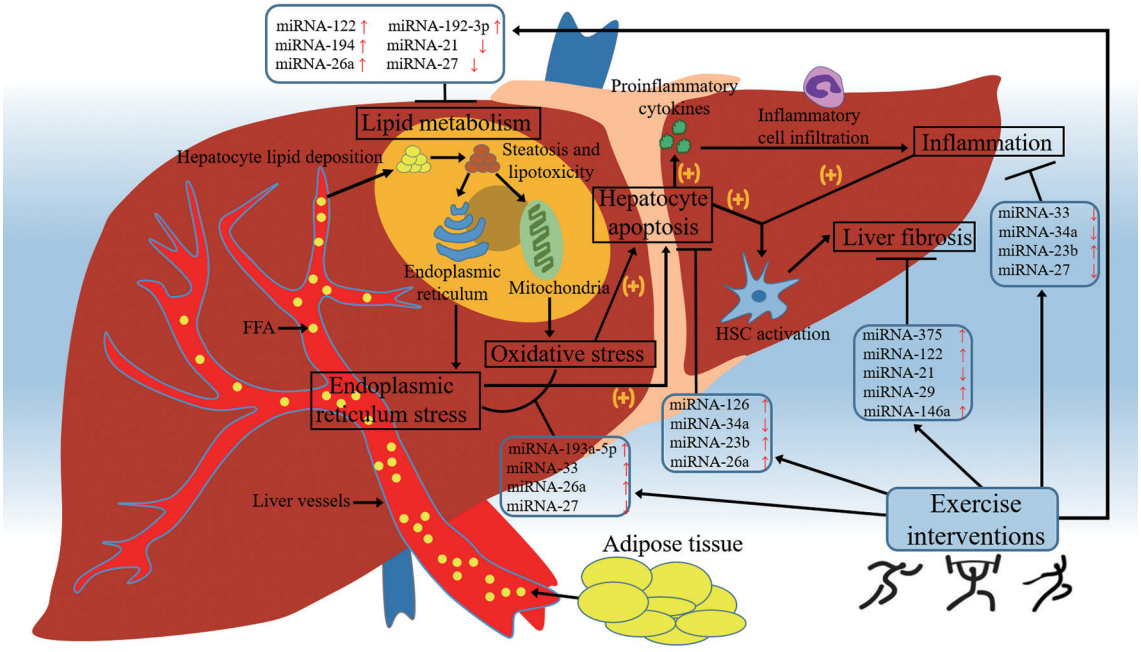
表1 不同类型的运动调控NAFLD相关miRNA的表达

Table 1 Different types of exercise regulate expression of miRNAs associated with NAFLD

机制 Mechanisms	研究对象 Object of study	运动类型与周期 Cycle and type of exercise	miRNAs	靶基因 Target gene	参考文献 References
Lipids metabolism	NAFLD mice	8-week aerobic exercise [A]	miRNA-122↑	*SREBP1*↓	[27-29]
	Obese rat	2-month aerobic exercise [B]	miRNA-192-3p↑	*GCR*↓	[30-31]
	Obese patient	3-month aerobic exercise [C]	miRNA-194↑	*Rac-1*↓, *Hmgcs*↓, *Apoa5*↓	[32-34]
	Obese patient	6-week aerobic exercise [D]	miRNA-21↓	*Fas*↓, *ACC*↓	[8,35]
	Healthy rat	10-week aerobic exercise [E]	miRNA-26a↑	*Akt/mTOR*↑	[36-38]
	Obese rat	4-week hypoxic exercise [F]	miRNA-27↓	*PPARγ*↑	[39-40]
Inflammation	Obese mice	8-week aerobic exercise [G]	miRNA-33↑	*ABCA1*↓	[46-47]
	NAFLD mice	12-week aerobic exercise [H]	miRNA-34a↓	—	[11,19]
	Healthy women	8-week aerobic combined with resistance exercise [I]	miRNA-23b↑	—	[20,48]
	Obese rat	4-week hypoxic exercise [F]	miRNA-27↓	*PPARγ*↑, *ABCA1*↓	[40,49-50]
Oxidative stress	Healthy male	72-hour sustained aerobic exercise [J]	miRNA-193a-5p↑	—	[10,56]
	Obese mice	10-week aerobic exercise [K]	miRNA-33↑	*SREBP1*↓	[57-58]
	Healthy rat	10-week aerobic exercise [E]	miRNA-26a↑	*EIF2α*↓	[36,38]
	Obese rat	4-week hypoxic exercise [F]	miRNA-27↓	*Nrf2*↑	[40,59]
Hepatocyte apoptosis	T2DM rat	6-week aerobic exercise [L]	miRNA-126↑	*Caspase-3*↓, *STAT3*↑	[63-65]
	NAFLD mice	12-week aerobic exercise [H]	miRNA-34a↓	*SIRT1*↑	[19,66-67]
	Healthy women	8-week aerobic combined with resistance exercise [I]	miRNA-23b↑	—	[20,48]
	Healthy rat	10-week aerobic exercise [E]	miRNA-26a↑	*SREBP1*↓, *IRE-1α*↓	[38,69]
Liver fibrosis	Male athletes	Long-term regular exercise	miRNA-375↑	*IGF-1*↑	[75-77]
	NAFLD mice	8-week aerobic exercise [A]	miRNA-122↑	*SREBP1*↓	[27,79-80]
	Obese rat	10-week aerobic exercise [M]	miRNA-21↓	*Bcl-2*↓, *PPARγ*↑	[9,81]
	Healthy rat	10-week aerobic exercise [N]	miRNA-29↑	*Dnmt3a*↓, *Dnmt3b*↓	[82-84]
	NAFLD patient	Long-term regular exercise	miRNA-146a↑	*TLR4/NF-κB*↓	[22]

↑: 表达上调; ↓: 表达下调; —: 未确定。A: 8周跑步运动, 1周5次, 每次60分钟, 50%最大速度; B: 2个月跑步运动, 1周5次, 每次60分钟, 速度为22米/分钟; C: 3个月有氧自行车运动, 1周3次, 前7周每次从20分钟渐增至50分钟, 第8周开始每次50分钟, 70%~80%最大心率; D: 6周循环测力计运动, 1周3次, 40%~60%最大摄氧量; E: 10周负重(5%体重)自由游泳运动, 1周5次, 每次60分钟; F: 4周低氧(13.6%氧浓度)跑步运动, 1周6次, 每次60分钟, 速度为20米/分钟; G: 8周跑步运动, 每次60分钟, 速度为20米/分钟; H: 12周跑步运动, 每次60分钟, 速度为15米/分钟; I: 8周有氧运动与阻抗运动联合训练, 有氧运动为跑步或者自行车, 阻抗运动为器械举重; J: 72小时内进行多次60~12分钟的中低强度(30%~65%最大摄氧量)的有氧运动, 每天3次, 其中2次为负重跑, 负重量为33.5千克, 1次为无负重跑; K: 10周跑步运动, 1周5次, 每次40分钟, 60%~65%最大摄氧量; L: 6周自由跑轮运动, 大鼠在铁笼内的跑轮装置中自由跑动, 可视作中低强度有氧运动; M: 10周负重(4%体重)自由游泳运动, 1周5次, 每次60分钟; N: 10周自由游泳运动, 1周5次, 每次60分钟。

↑: expression rising; ↓: expression decreasing; —: not determined. A: eight weeks of running exercise, five times a week for 60 min at 50% of maximal speed; B: two months of running exercise, five times a week, one time for 60 min at 22 m/min; C: three months of aerobic cycling exercise, three times a week, tapering from 20 to 50 min each time for the first seven weeks, and 50 min each time at 70% to 80% maximal heart rate starting in week eight; D: six weeks of cycle ergometer exercise, three times a week, 40%-60% of maximal oxygen uptake; E: ten weeks of weight-bearing (5% of body weight) free swimming exercise, five times a week, one time for 60 min; F: four weeks of low-oxygen (13.6% of oxygen concentration) running exercise, six times a week, one time for 60 min at a speed of 20 m/min; G: eight weeks of running exercise, one time for 60 min at a speed of 20 m/min; H: 12 weeks of running exercise, one time for 60 min at a speed of 15 m/min; I: eight weeks of combined aerobic and impedance exercise, with running or cycling for aerobic exercise and weight lifting on machines for impedance exercise; J: multiple 60-12 min sessions of low- and moderate-intensity (30%-65% of maximal oxygen uptake) aerobic exercise, three times a day over 72 hours, two of which were weighted runs with a weight of 33.5 kg, and one of which was unweighted; K: ten weeks of running exercise, five times a week, one time for 40 min at 60%-65% of maximal oxygen uptake; L: six weeks of free-running wheel exercise, where the rats ran freely on a running wheel device in an iron cage, which could be regarded as low- and moderate-intensity aerobic exercise; M: ten weeks of weight-bearing (4% of body weight) free-swimming exercise, five times a week, one time for 60 min; N: ten weeks of free-swimming exercise, five times a week, one time for 60 min.



(+): 加快病情发展; ↑: 表达上调; ↓: 表达下调。

(+): promote the development of symptoms; ↑: expression rising; ↓: expression decreasing.

图3 运动调控相关miRNA改善NAFLD的机制示意图

Fig.3 Schematic diagram of the mechanism of exercise regulation-related miRNAs for the treatment of NAFLD

氧化应激, 扰乱线粒体蛋白环境并加剧线粒体损伤, 破坏细胞DNA、蛋白质等分子[52]。氧化应激被视作NAFLD病程中肝细胞发生内质网应激、炎症反应、凋亡的诱因, 其中内质网应激可与氧化应激相互作用, 加快NAFLD的病情发展[53], 因此,干预氧化应激相关miRNA的表达, 抑制肝脏氧化应激以恢复机体的正常脂质代谢是治疗NAFLD的方法之一[2,54-55]。

JOHNSON等[10]研究发现NAFLD病程中miRNA-193a-5p表达水平增加, 可减轻患者肝脏细胞氧化应激, 而72小时内连续性的有氧运动使得人体miRNA-193a-5p循环水平提高, 且miRNA-193a-5p循环水平与运动时长呈正相关[56], 这提示运动可以通过提升miRNA-193a-5p水平的方式来改善NAFLD患者的氧化应激, 但miRNA-193a-5p所涉及的靶基因与下游因子仍不明确。miRNA-33是诱导脂质生成信号转导的重要调节因子, 肝脏中miRNA-33表达水平过低会导致脂质合成量上升并激活*SREBP1*, 导致氧化应激现象出现, 致使肝细胞死亡[57], 研究显示10周中高强度有氧运动能上调NAFLD小鼠的miRNA-33表达, 改善脂质合成与氧化应激情况[58]。miRNA-26a可直接介导肝细胞真核起始因子2α(eukaryotic initiation factor 2α, *EIF2α*)(诱导细胞内质网应激的关键基因), 上调miRNA-26a表达可抑制*EIF2α*过表达, 减轻内质网应激与肝脏脂质变性[36]。长期规律的有氧运动能逆转NAFLD患者肝脏miRNA-26a的低水平现象, 进而减少内质网应激情况[38]。上文提及的*Nrf2*也是提升细胞抗氧化应激能力的关键因子, miRNA-27过表达可靶向抑制*Nrf2*表达[59], 因此, 运动通过抑制miRNA-27表达提升*Nrf2*的表达水平, 有益于NAFLD患者提升肝细胞抗氧化应激能力(表1)。以上结果提示, 肝脏ROS过量诱发的氧化应激加速NAFLD发展, 而运动可通过调控氧化应激相关miRNA的表达, 抑制诱发内质网应激的基因表达, 提升抗氧化因子水平, 减弱内质网应激与氧化应激的相互作用, 提升细胞抗氧化应激能力并恢复正常脂质代谢水平, 从而改善NAFLD(图3)。需要注意的是, 氧化应激相关miRNA所靶向的下游基因研究尚少, 诸多机制尚未明确。因此, 运动调控相关miRNA表达以抑制NAFLD氧化应激的机制仍有巨大的探究空间。

2.4 运动调控miRNA表达改善NAFLD病程中的肝细胞凋亡

在NAFLD病程中常见肝细胞凋亡现象。炎症反应、氧化应激等损伤因素会导致肝细胞出现过度凋亡现象, 从而刺激肝脏炎症反应与纤维化的发生,

加速NAFLD的病程发展[60]。通过调控相关miRNA表达以抑制肝细胞过度凋亡可为NAFLD治疗提供新思路。

miRNA的表达对于介导肝细胞凋亡的B细胞淋巴瘤-2(B cell lymphoma-2, *Bcl-2*)、半胱氨酸天冬氨酸蛋白酶-3(cysteine-aspartate-specific protease-3, *Caspase-3*)等基因有一定作用[61-62]。抑制*Caspase-3*表达可有效减少NAFLD个体肝细胞凋亡数量[63], 通过体外细胞对比实验发现miRNA-126的过表达可激活信号转导和转录激活因子3(signal transducer and activator of transcription 3, *STAT3*)并抑制*Caspase-3*表达[64], 此外, miRNA-126激活*STAT3*也可有效预防*Fas*介导的氧化应激。而CHODAR等[65]发现6周中低强度有氧运动显著提升了大鼠的miRNA-126表达水平, 这提示运动可促进miRNA-126表达激活*STAT3*并抑制*Caspase-3*, 以减轻NAFLD病程中的氧化应激与肝细胞凋亡。另有研究发现NAFLD患者肝脏中miRNA-34a靶向抑制沉默信息调节因子1(silence information regulator 1, *SIRT1*), 促使肝细胞凋亡, 并与病情严重程度呈正相关[66-67], 其他研究也显示miRNA-34a对于肝细胞具有促凋亡作用[68]。运动在上调NAFLD肝细胞中ADA表达的同时显著抑制miRNA-34a表达, 这提示运动可通过抑制miRNA-34a提升靶基因*SIRT1*表达水平, 从而缓解炎症反应与肝细胞凋亡[19]。前文中提及的miRNA-23b对于肝细胞异常凋亡有抑制作用[48], 而运动干预可以有效提升miRNA-23b的表达水平[20], 以抑制肝细胞异常凋亡。提升miRNA-26a表达水平能够降低NAFLD个体的游离脂肪酸(free fatty acid, FFA)、TG水平, 抑制靶基因*SREBP1*、肌醇依赖性激酶1α(inositol-requiring enzyme-1α, *IRE-1α*)(*IRE-1α*高表达可促使肝细胞内质网应激与细胞凋亡)的表达, 提升肝脏细胞的抗氧化应激能力以抑制其异常凋亡[69], 而运动可以有效促进miRNA-26a的表达[38](表1)。总之, NAFLD病程中的炎症反应、氧化应激等不利因素均会造成肝细胞过度凋亡, 加速病情发展, 而miRNA-126、miRNA-34a等表达均受运动调控, 这些miRNA可通过作用于如*SIRT1*、*Caspase-3*等上下游基因, 以抑制肝脏细胞的过度凋亡从而改善NAFLD(图3)。

2.5 运动调控miRNA表达改善NAFLD病程中的肝纤维化

肝纤维化是指由于肝细胞外基质积累及持续性损伤修复导致肝内形成大量异常瘢痕组织的病理现象[70], 若未及时干预, 其会发展为LC、HCC。因此, 肝纤维化被视为NAFLD病情评估的重要指标之一[71]。在NAFLD病程中, 受损肝细胞促进巨噬细胞、HSC释放大量不同的炎症因子与促纤维化介质, 导致炎症免疫细胞进入肝脏组织, 激活可产生细胞外基质的细胞群, 造成细胞外基质蛋白沉积并驱动纤维性瘢痕组织形成[42,72-74]。肝纤维化通过一定手段可被逆转, 而在肝纤维化逆转过程中, 诸多miRNA表达水平也受到运动的影响。

miRNA-375的高表达对于NAFLD肝纤维化有抑制作用[75-76], 长期运动者miRNA-375表达呈高水平, 高表达水平的miRNA-375可介导胰岛素样生长因子(insulin-like growth factor, *IGF-1*)表达水平提升, *IGF-1*水平的提升加速肝脏脂质消耗并消除纤维性组织[77-78], 这提示NAFLD患者可通过长期运动上调miRNA-375表达, 并提升*IGF-1*水平, 以抑制肝脏纤维化。miRNA-122表达缺失会使小鼠发生严重的肝脏脂质变性并导致NASH, 进而引起肝纤维化症状的出现, 这提示miRNA-122在NAFLD病程中起到重要作用[79]。短期内的运动会造成miRNA-122表达水平下降, 但8周中等强度有氧运动会使得NAFLD小鼠肝脏miRNA-122水平上升[27,80], 进而降低*SREBP1*、IL-6、TNF-α的表达水平, 并抑制小鼠炎症反应与胰岛素抵抗, 以上提示miRNA-122受运动调控后抑制*SREBP1*等靶基因, 对于缓解NAFLD炎症反应、肝纤维化等有重要意义。抑制miRNA-21可激活*PPARγ*的表达来减轻炎症、肝损伤和纤维化[81], 10周的负重(4%体重)有氧运动可降低miRNA-21水平, 继而抑制肝细胞凋亡基因*Bcl-2*表达, 同时上调*PPARγ*表达水平以缓解肝纤维化症状[9]。miRNA-29抑制剂会使得靶基因DNA甲基转移酶3a(DNA methyltransferase 3a, *Dnmt3a*)、DNA甲基转移酶3b(DNA methyltransferase 3b, *Dnmt3b*)表达上调(*Dnmt3a*、*Dnmt3b*基因表达上调可促使小鼠HSC活化增殖, 诱发肝纤维化现象)[82-83], 10周低强度有氧运动会使得miRNA-29的表达上调[84], 由以上研究结果推测运动可提升miRNA-29表达水平, 并对NAFLD肝纤维化逆转起一定作用。Toll样受体4/核因子-κB(Toll-like receptor 4/nuclear factor κB, TLR4/NF-κB)信号通路过表达会活化HSC诱发肝纤维化, 彭丹等[22]发现长期规律运动可促进miRNA-

146a的表达, 靶向下调TLR4/NF-κB信号通路相关基因水平, 从而减轻NAFLD个体的炎症反应与肝纤维化(表1)。综上所述, NAFLD病程中的肝纤维化由持续性炎症反应及瘢痕组织积累造成, 而肝纤维化形成过程受到相关miRNA的调控。这提示运动可通过调控炎症反应或肝纤维化相关miRNA表达, 减少炎症因子或者清除肝组织内基质蛋白, 直接或间接逆转NAFLD肝纤维化, 以治疗NAFLD(图3)。目前有研究指出运动可作为逆转肝纤维化的手段之一, 但其具体机制研究仍有不足, 或许运动调控NAFLD病程中相关miRNA的表达可作为解释该机制的新思路。

3 总结与展望

有氧运动、阻抗运动、高强度间歇运动对于肝细胞脂代谢、炎症反应、氧化应激、肝细胞凋亡等均有改善作用, 但将某项运动单独作为干预方案效果是不够理想的, 综合多种方案结合患者身体情况制定运动处方是最佳的选择[85]。一定强度的运动对于肝脏表现是有益的, 但是合适的运动量与方案制定(包括最佳体力活动频率、持续时间或强度等)还需要更深入的研究[86]。

对于运动治疗NAFLD的机制尚未完全明确, 但运动通过调控miRNA表达改善NAFLD为解释该机制提供了新启示。运动干预治疗NAFLD过程中, 运动对于某些miRNA表达具有调控作用, 这些miRNA的表达水平对于NAFLD病程发展有一定影响, 这提示运动治疗NAFLD的过程, 必然与相关miRNA表达存在联系。在运动调控相关miRNA表达治疗NAFLD的机制中, 改善脂质代谢、抑制炎症反应、提升抗氧化应激能力、减少肝细胞凋亡、实现肝纤维化逆转是关键。此外, 深入探究相关miRNA表达所涉及的信号通路及靶向的上下游基因, 对于进一步理解NAFLD治疗机制同样具有重要的理论与实践意义。

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