PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2024, 51(8): 1873~1882
www.pibb.ac.cn

鸢尾素改善肝脏脂质代谢紊乱减轻非酒精性脂肪性肝病的研究现状*

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摘要　肝脏大量脂质蓄积是非酒精性脂肪性肝病（nonalcoholic fatty liver disease，NAFLD）的重要病理特征。肝脏脂质摄取、脂质从头合成、脂肪酸氧化分解和脂质分泌输出这4个环节间的失衡是造成肝脏脂质蓄积的重要原因。运动具有改善脂质代谢，缓解NAFLD发展的作用，但其机制复杂尚未完全阐明。肌肉不仅是运动器官，还是重要的内分泌器官，一系列介导运动促进健康效应的内分泌因子主要由肌肉产生。鸢尾素（Irisin）是主要由肌肉分泌的内分泌因子，其合成和分泌受运动调节，可靶向机体多种器官组织，发挥改善NAFLD等肥胖相关慢性代谢性疾病的作用。Irisin改善NAFLD的效应与其对脂质代谢的积极调控作用密不可分。本文阐述了运动调控Irisin合成与分泌的可能机制，并对Irisin改善上述4个肝脏脂质代谢的重要环节、减轻NAFLD的研究进展进行了总结，同时提出其中尚需进一步明确的问题，以期更好地理解Irisin介导运动在NAFLD等代谢疾病中的作用。

关键词　鸢尾素，运动，非酒精性脂肪性肝病，脂代谢
中图分类号　G804，R87　　**DOI**：10.16476/j.pibb.2023.0359

随着能量过度摄入和久坐生活方式的流行，全球非酒精性脂肪性肝病（nonalcoholic fatty liver disease，NAFLD）的发病率持续攀升。中国是NAFLD患病率增长最快的国家之一[1]。据预测，中国NAFLD患病人数将从2016年的2.4亿增加到2030年的3.1亿[2]。NAFLD的疾病谱包括单纯性脂肪肝（nonalcoholic simple fatty liver，NAFL）、非酒精性脂肪性肝炎（nonalcoholic steatohepatitis，NASH）以及其相关肝硬化和肝细胞癌。NAFLD的病理进展遵循“三击”过程，即脂肪变性、脂质毒性和炎症反应[3]。除对肝脏具有危害外，NAFLD也显著增加了多种肝外并发症的发生率，如2型糖尿病、心血管疾病、慢性肾脏疾病以及一些肝外恶性肿瘤[4]。尽管近年来NAFLD的发病机制、治疗靶点以及药物开发的研究工作取得了显著进展，但目前NAFLD仍缺乏特效药物。大量研究表明，运动作为一种低成本且无副作用的干预方式可有效改善NAFLD。改善脂质代谢是运动防治NAFLD的关键机制。研究表明，运动对肝脏摄取循环中的游离脂肪酸（free fatty acid，FFA）[5]、脂质从头合成（*de novo* lipogenesis，DNL）[6]、脂肪酸氧化（fatty acid oxidation，FAO）分解[7]和肝脏脂质分泌输出[6]这4个肝脏脂质代谢的重要环节均有良好的调节作用。骨骼肌不仅是主要的运动器官，还是重要的内分泌器官。运动产生的健康效应与肌肉分泌的内分泌因子密不可分，近年来运动调控的内分泌因子鸢尾素（Irisin）因其可有效改善肥胖相关慢性代谢性疾病受到学者们的广泛关注。Irisin是Boström等[8]于2012年在肌细胞中发现的一种受过氧化物酶体增殖物激活受体γ辅助激活因子1α（peroxisome proliferator activated receptor-γ coactivator-1α，PGC-1α）调控的内分泌因子，研究发现其可促进脂肪组织棕色化。后续的研究陆续发现，Irisin除了对脂肪组织起作用外，

* 广东省普通高校特色创新类项目（2021KTSCX059）资助。
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收稿日期：2023-09-13，接受日期：2024-03-15

还可靶向肝脏、骨骼肌、骨骼等多种组织器官，发挥改善糖脂代谢[9-10]、调节骨骼肌再生[11]、促进骨骼重塑[12]等多种积极的健康效应。研究提示，Irisin在运动改善NAFLD中起重要作用。肝脏脂质代谢异常是NAFLD发生发展的关键机制，本文就Irisin调控肝脏脂质代谢改善NAFLD进行阐述。

1 运动提高循环Irisin水平

Irisin是由III型纤维连接蛋白结构域包含蛋白5（fibronectin type III domain containing protein 5，FNDC5）经蛋白酶水解释放的分泌结构域。FNDC5在骨骼肌中高表达，在心脏、舌和直肠等含有肌肉的组织器官中也有较高的表达水平[13]。脂肪组织、肝脏、中枢神经系统、肾脏、甲状腺也均可表达FNDC5[14]，但在肝脏中FNDC5表达水平低[13]。

循环Irisin约70%由肌肉分泌[14]，增加FNDC5表达和促进FNDC5酶切释放Irisin均可提高循环Irisin水平。2012年Pontus Boström团队[8]发现，运动通过转录因子PGC1-α促进骨骼肌表达FNDC5，提高循环Irisin水平，运动调控Irisin合成与分泌过程如图1所示。后续大量的动物和人群运动干预研究亦证实，游泳[15]、跑台训练[16]、长跑[17]等有氧运动后，循环Irisin水平约能提升27%~65%，经过12周的抗阻训练后，运动组较对照组的循环Irisin水平增加约1.4倍[18]。值得注意的是，尽管Boström等的研究显示，运动诱导循环中Irisin的增加水平大致与骨骼肌中FNDC5 mRNA的增加水平呈比例，Pang等[19]的研究却发现，小鼠循环Irisin水平在运动过程中升高，运动结束1 h下降，随后缓慢上升，在运动结束6 h后达到峰值，而FNDC5水平在运动后2 h升至最高水平，随后下降。运动诱导的Irisin与FNDC5变化的不一致表明，除增加FNDC5表达外，运动可能通过促进FNDC5蛋白酶切增加Irisin的分泌。FNDC5酶切形成Irisin是个复杂的过程，Yu等[20]证实此作用部分依赖于解聚素金属蛋白酶（a disintegrin and metalloproteinases，ADAMs）家族中的ADAM10，但运动是否参与此过程仍需进一步研究。Aydin等[21]予以大鼠游泳干预，发现心肌比骨骼肌产生更多的Irisin。骨骼肌是否是运动诱导循环Irisin增加的主要来源也需进一步探讨。

除运动外，Irisin水平还受饮食（糖、脂质）、温度、内分泌因子和药物等影响[22-23]。体外研究证实，棕榈酸和高糖对肌细胞FNDC5抑制率分别达40%和20%[24]。而2型糖尿病患者肌细胞FNDC5水平却显著升高，表明糖和脂质对Irisin的调控还受其他因素的影响。肌肉因子Myostatin具有降低Irisin水平的作用，而低温、药物（非诺贝特、二甲双胍）可提高Irisin水平[22]。

利用*FNDC5*基因敲除小鼠实验，研究者们已证实，Irisin在运动促进包括肝脏在内的多器官组织健康中发挥着重要的作用：运动可有效激活FNDC5/Irisin-PI3K/Akt信号通路，抑制心梗后肝脏的炎症反应[25]；运动减轻心梗诱发的骨骼肌氧化应激和凋亡的作用也部分依赖于Irisin[26]；运动还可通过Irisin发挥降低血管僵硬度并提高骨骼硬度[27]等作用。

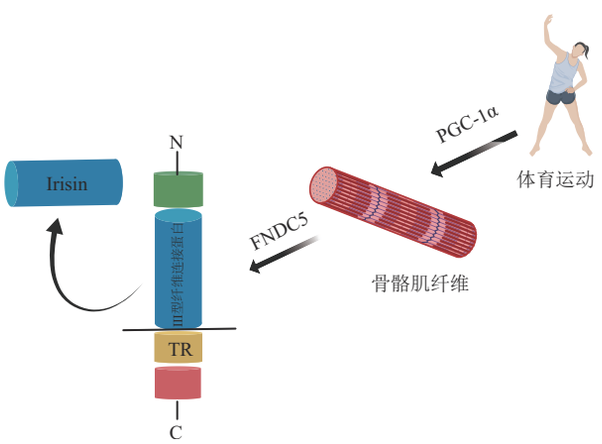

Fig. 1 Exercise regulates Irisin synthesis and secretion[28]

图1 运动调控Irisin合成与分泌[28]

TR：跨膜区（transmembrane region）。

2 Irisin调节脂质代谢改善NAFLD

肝脏大量脂质聚积是NAFLD的标志性病理改变。肝脏是脂质代谢的重要器官。肝脏脂质积累是脂质摄取、脂质合成、脂质利用和脂质输出间的不平衡造成的，肝脏脂质稳态的调节主要包括以下4方面：循环脂质的摄取、DNL、FAO和极低密度脂蛋白（very low-density lipoprotein，VLDL）介导的脂质输出。这些途径中的一种或多种的破坏均可能导致脂质在肝脏中的滞留以及随后NAFLD的发展，Irisin改善肝脏脂质代谢紊乱的各个环节如图2所示。研究报道，循环Irisin水平与肝内甘油三酯（triglyceride，TG）含量呈负相关[29]，提示Irisin在改善NAFLD肝脏脂质代谢中发挥重要作

用。*FNDC5*敲除和Irisin干预实验为上述观点提供了更有力的佐证：*FNDC5*基因敲除小鼠表现出糖脂代谢紊乱，循环低密度脂蛋白-胆固醇水平升高，高密度脂蛋白-胆固醇水平降低，胰岛素敏感性明显下降，肝脏脂肪变性加重[30-31]；一周的Irisin干预则可显著降低甲硫氨酸和胆碱缺乏（methionine and choline deficient，MCD）饮食诱导的NAFLD小鼠血清丙氨酸氨基转移酶（alanine aminotransferase，ALT）、天冬氨酸转氨酶（aspartate aminotransferase，AST）水平降低，并有效减少肝脏脂质聚集[9]。除了降低肝脏脂质蓄积外，Irisin可减轻肝脏巨噬细胞聚集，降低IL-1β、IL-6和TNF-α等炎症因子水平，抑制肝星状细胞增殖、迁移、收缩与活化，减少肝星状细胞释放促纤维化外泌体，减轻肝纤维化程度，对MCD膳食和四氯化碳诱导的NASH均有显著的改善效果[9，32-34]。脂质代谢紊乱是NAFLD的主要病理特征和重要发病机制，下文就Irisin在调节肝脏摄取、脂质合成、脂质利用和脂质输出，改善NAFLD中的作用展开阐述。

2.1　Irisin与肝脏脂肪酸摄取

正常情况下肝脏并不是储存脂质的主要场所，机体的脂质主要储存在脂肪组织中；病理条件下，脂肪组织脂质代谢紊乱，发生纤维化，出现异位脂质沉积，脂质积蓄在肝脏、胰腺、肌肉等部位。减少肝脏脂质摄取，改善脂肪组织脂质代谢紊乱，增加其储存脂质的能力，增加骨骼肌对脂肪酸的摄取消耗均有助于减少肝脏外源性脂肪酸的输入。

2.1.1　Irisin对肝脏FFA摄取相关蛋白的作用仍不清楚

肝脏过度摄取循环中FFA是肝脏脂质代谢紊乱的一个重要特征，可推动NAFLD的发展。肝脏吸收血液中的FFA很大程度上依赖于脂肪酸转运蛋白，而FFA被动扩散进入肝脏的量较少[35]。肝细胞对FFA的摄取主要由脂肪酸转运蛋白（fatty acid transport protein，FATP）、小窝蛋白、脂肪酸转位酶（fatty acid translocase，FAT/CD36）和脂肪酸结合蛋白（fatty acid binding proteins，FABP）介导。

尽管目前尚未见关于Irisin对肝脏FFA摄取的针对性研究，但已有研究表明，长期运动可抑制肝脏FFA摄取相关蛋白的表达。16周的跑台运动显著降低高脂高果糖诱导的NASH小鼠肝脏约36%的*CD36* mRNA表达[36]；12周的游泳干预减少了高脂喂养小鼠肝脏FABP主要亚型FABP1蛋白约56%的表达，值得注意的是，运动减轻肝脏TG、总胆固醇（total cholesterol，TC）积蓄的作用在肝脏特异性过表达FABP1小鼠中明显减弱，提示FABP1在运动改善肝脏脂质代谢中的重要作用[37]；Irisin是否参与上述运动对肝脏FFA摄取相关蛋白表达的抑制作用仍不清楚。Irisin可否通过抑制肝脏FFA摄取相关蛋白的表达发挥降低肝脏FFA摄取减轻NAFLD的作用也需进一步探讨。

2.1.2　Irisin促进脂肪组织和骨骼肌的脂质代谢

脂肪组织、骨骼肌分别作为机体主要的脂质储存和消耗场所，其脂质代谢的改善有助于减少肝脏脂质的输入。2012年Boström等[8]发现Irisin并证实其具有促进白色脂肪棕色化增进脂肪组织产热的作用。Irisin介导脂肪组织棕色化的机制涉及增加过氧化物酶体增殖物激活受体α（peroxisome proliferators-activated receptors α，PPARα）的表达与促进p38丝裂原活蛋白激酶（p38 mitogen-activated protein kinase，p38 MAPK）和细胞外信号调节激酶（extracellular signal-related kinase，ERK）的磷酸化[8，38]。随后的研究表明，除脂肪组织外，骨骼肌亦是Irisin的重要靶组织，Irisin通过提高AMP依赖蛋白激酶（adenosine 5'-monophosphate-activated protein kinase，AMPK）磷酸化水平促进骨骼肌脂肪酸β氧化[39-40]。Irisin可否抑制脂肪组织纤维化增进其储脂能力，又是否能提高骨骼肌对循环FFA的摄取进而减少肝脏FFA输入尚需进一步研究。

2.2　Irisin抑制肝脏DNL

除了摄取循环中的FFA外，DNL亦是肝脏脂质的重要来源。DNL是利用碳水化合物和氨基酸中的碳转化为脂质的过程，可以分为3个连续的步骤：脂肪酸合成、脂肪酸碳链延长/去饱和与组装成TG[41]。这个过程涉及的关键酶包括乙酰辅酶A羧化酶（acetyl-coenzyme carboxylase，ACC）、脂肪酸合成酶（fatty acid synthase，FAS）、硬脂酰辅酶a去饱和酶1（stearoyl-CoA desaturase-1，SCD-1）和甘油二酯酰基转移酶2（diacylglycerol acyltransferase-2，DGAT2）。

Donnelly等[42]的研究表明，NAFLD患者肝内TG中的59%源自肝脏对体内脂解脂肪酸的摄取，15%源自膳食，此外还有26%来自肝脏DNL。肝脏DNL增加是NAFLD的显著特征。Lambert等[43]发现，NAFLD患者与同等身体质量指数（body

mass index，BMI）对照组相比肝脏DNL增加约3倍。近年研究亦显示，肝脏DNL对瘦体重、正常肥胖和肥胖并伴随NAFLD人群肝内TG的贡献率分别为11%、19%和38%[44]。肝脏DNL的增加是推动NAFLD发展的重要机制。研究表明，靶向DNL关键酶可降低NAFLD肝脏脂质蓄积。动物实验证实，肝脏特异性ACC抑制剂给药6 d可减少20%DNL生成，长期给药治疗显著降低高脂高糖饮食诱导的肝脏脂质蓄积[45]。人群研究亦显示，予以NAFLD人群一个月肝脏特异性ACC抑制剂干预可降低肝脏36%的TG含量[46]。抑制DGAT2可使肝细胞TG含量减少50%，减轻膳食诱导的肝脏脂肪变性[47-48]。此外，抑制调控DNL的关键转录因子固醇调节元件结合蛋白1（sterol regulatory element binding protein 1，SREBP-1）和碳水化合物反应元件结合蛋白（carbohydrate response element binding protein，ChREBP）的表达也可抑制DNL，改善NAFLD。

Gaggini等[49]研究表明，肝细胞癌患者肝脏*FNDC5* mRNA水平与肝脏DNL相关基因*SCD-1*和*SREBP-1*的mRNA水平具有较强的相关性，提示Irisin在调控肝脏DNL中发挥着重要的作用。利用FNDC5敲除和过表达动物，研究人员证实了Irisin具有抑制肝脏DNL的作用。在高脂饮食条件下，FNDC5敲除小鼠肝脏DNL相关基因*SREBP1*、*FAS*、*SCD-1*和*DGAT-1*水平均显著上升，而上述基因的表达在FNDC5过表达小鼠中明显降低[31]。在进一步的细胞和动物实验研究中，Irisin抑制DNL的机制得到了揭示。在高糖高胰岛素条件下，Irisin可通过磷酸化肝激酶B1（liver kinase B1，LKB1）提高AMPK/ACC磷酸化水平，降低HepG2细胞TG含量[50]。除了通过磷酸化降低DNL相关酶的活性外，Irisin还可减少调控DNL的关键转录因子肝脏X受体（liver X receptor，LXRα）和SREBP-1的表达、核转位与转录活性[51]，提高AMPK活性抑制雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）[31]，进而减少DNL相关酶ACC和FAS的表达。

2.3 Irisin抑制肝脏脂肪酸β氧化

肝脏是进行脂肪酸氧化最活跃的组织之一，其中脂肪酸β氧化发生在线粒体和过氧化物酶体中。线粒体脂肪酸β氧化可将脂肪酸逐渐缩短形成乙酰辅酶A。乙酰辅酶A或可被进一步代谢生成酮体供肝外组织作为可氧化的能量底物使用，或可进入三羧酸循环被进一步氧化生成水和二氧化碳并释放能量[52]。脂肪酸β氧化的速率受肉碱棕榈酰转移酶1（carnitine palmitoyl transferase-1，CPT-1）（介导脂肪酸线粒体转运）以及后续脂肪酸β氧化相关链酰基辅酶A脱氢酶（acyl-CoA dehydrogenase，ACADM）（介导β氧化第1步）和微粒甘油三酯转移蛋白（microsomal triglyceride transfer protein，MTP）（介导β氧化的2~4步）的调控。已有大量动物研究利用基因干预手段调控脂肪酸β氧化的相关酶，证实了脂肪酸β氧化受损是推动NAFLD发展的重要因素。中链和极长链ACADM缺陷小鼠脂肪酸β氧化受损，表现出显著的肝脏脂肪变性；*MTP-α*$^{-/-}$小鼠自出生起就出现肝脏脂肪变性，*MTP-α*$^{+/-}$小鼠也在后续的喂养阶段出现了明显的肝脏脂质蓄积[52]。人群研究亦显示，NASH患者脂肪酸β氧化相关酶活性较正常人群显著降低[53]。

研究发现，许多增加脂肪酸β氧化相关酶表达的物质，同时也具有提高Irisin水平的能力。玉米黄质增加了高脂饮食喂养小鼠脂肪酸β氧化酶（CPT-1、CPT-2、ACADM）的表达和血清Irisin的水平[54]；视黄酸刺激肌细胞脂肪酸β氧化相关蛋白表达的同时增强Irisin的分泌[55]；在高脂饮食喂养条件下，植物乳杆菌显著增强了肝脏和脂肪组织中PPARα、CPT1、酰基辅酶A氧化酶1（acyl-coa oxidase-1，ACOX1）的表达并提高肌肉Irisin的mRNA水平[56]。这些结果提示Irisin和脂肪酸β氧化存在相关性。已有研究为Irisin及其前体FNDC5通过抑制肝脏脂肪酸β氧化减轻肝脏脂质蓄积提供了更直接的证据。*FNDC5*敲除小鼠肝脏脂肪酸β氧化酶CPT-1和ACOX-1的表达减少，肝脏出现严重的脂肪变性，外源性添加FNDC5则可恢复肝细胞脂肪酸β氧化相关酶的表达，并改善棕榈酸诱导的*FNDC5*$^{-/-}$肝细胞的脂肪变性[31]。目前关于FNDC5/Irisin上调β氧化相关酶增加肝脏脂肪酸β氧化的机制仍未完全阐明。Liu等[31]的研究发现，能量剥夺诱导的脂肪酸氧化和AMPK活性的提高在*FNDC5*$^{-/-}$肝细胞中明显减弱，利用5-氨基咪唑-4-甲酰胺核糖核苷酸（5-aminoimidazole-4-carboxamide ribonucleotide，AICAR）激活AMPK则可恢复肝细胞脂肪酸氧化；同时，他们还发现，抑制mTORC1显著增加*FNDC5*$^{-/-}$小鼠肝脏脂肪酸氧化，减轻肝脏脂肪变性。这些结果提示，FNDC5/Irisin可能通过提高AMPK活性，抑制mTORC1，发挥降低肝脏脂肪酸氧化的作用。

2.4　Irisin对肝脏脂质输出的作用仍不清楚

肝细胞摄取的脂肪酸与来自DNL的脂肪酸用于TG和其他复杂脂质的合成。TG一部分储存在脂滴中，另一部分TG主要通过与载脂蛋白B（apolipoprotein B，APOB）结合形成VLDL-TG的形式，输出到循环中。这一过程受微粒TG转移蛋白（microsomal TG transfer protein，MTTP）和诱导细胞死亡DFF45样效应子B（cell death-inducing DFF45-like effector B，CideB）等蛋白质的调节。NAFLD状态下，肝内脂质的增多使用于合成VLDL-TG的底物增加，同时胰岛素抑制VLDL-TG分泌的能力减弱，致使肝脏VLDL-TG的输出增加[57]，加重高甘油三酯血症。Irisin可改善TG代谢。*FNDC5*敲除可使正常饮食小鼠和高脂饮食小鼠循环TG含量显著增加，而FNDC5过表达则明显降低高脂饮食小鼠血清TG水平[31]。尽管目前尚未见关于Irisin对肝脏VLDL-TG分泌率的影响研究，但Canivet等[58]的研究表明，通过siRNA抑制FNDC5表达显著降低小鼠原代肝细胞和HepG2细胞VLDL-TG合成相关蛋白APOB和CideB的mRNA水平，提示Irisin可能具有促进肝脏VLDL-TG输出的功能。

2.5　Irisin改善胰岛素抵抗

胰岛素抵抗推动NAFLD的发生发展。当机体处于胰岛素抵抗状态时，胰岛素代偿性地分泌增加，过高的胰岛素可促进肝脏DNL，刺激肝细胞脂肪酸摄取[44，59-60]，进而加重肝脏脂质蓄积。研究人员利用基因编辑技术去除全身Irisin和Irisin干预实验在饮食与基因诱导的糖尿病小鼠中证实了Irisin具有改善胰岛素抵抗的作用[61-62]。体外研究亦证实，Irisin可提高肝细胞胰岛素诱导的Akt、GSK3α/β和FoxO1的磷酸化水平，改善胰岛素抵抗[50]。除肝细胞外，Irisin还可减轻胰岛β细胞、成肌细胞、心肌细胞的胰岛素抵抗[63-65]。目前研究已证实Irisin减轻胰岛素抵抗的机制涉及激活AMPK、p38-MAPK-PGC-1α和PI3K-AKT-FOXO1通路[50，64-65]。减轻胰岛素抵抗可能是Irisin改善肝脏脂质代谢的重要机制。

3　NAFLD患者循环及肝脏Irisin水平

已有许多研究团队对NAFLD患者循环Irisin水平进行检测。2013年Zhang等[29]的研究表明，与非NAFLD人群相比，NAFLD患者血清Irisin水平显著降低；他们还发现，血清Irisin水平随着肝内TG含量的增加而降低。随后2014年Polyzos研究团队[66]报道，与瘦体重对照组相比，单纯性脂肪肝和NASH患者血清Irisin水平均显著降低，但NAFL组、NASH组与肥胖对照组3组间血清Irisin水平却无显著差异。2022年Ulualan等[67]的研究也表明，与肥胖对照组相比，NAFLD患者血清Irisin水平并无显著变化。然而，在Choi研究团队[68]和Kosmalski[69]研究团队的报道中，与非NAFLD对照组相比，NAFLD患者循环Irisin水平均显著升高。值得注意的是，Armandi等[70]在近期的研究中发现NASH患者循环Irisin水平随着纤维化程度的加剧而升高，而在Choi等[68]的报道中，相较于中至重度NAFLD患者，轻度NAFLD患者具有更高的循环Irisin水平。上述研究结果的不一致引人深思。这些差异提示循环及肝脏Irisin水平与NAFLD间的关系复杂。肥胖、NAFLD脂质代谢紊乱、不同干预方式与炎症程度乃至种族[71]均可能是造成这些差异的原因。已有学者提出了Irisin抵抗的假设，推测由于肥胖和相关慢病Irisin敏感性降低，机体代偿性的产生和分泌更多的Irisin，致使循环Irisin水平升高[72-73]。NAFLD患者循环Irisin水平升高的研究结果是否由于Irisin抵抗而造成亦是值得研究的问题。

关于NAFLD肝脏FNDC5表达和Irisin水平的研究则取得了较一致的结果。Canivet等[58]检测了高脂饮食和MCD饮食诱导的两种NAFLD小鼠和NAFLD人群肝脏FNDC5表达情况，发现NAFLD动物和人群均出现肝脏FNDC5表达的升高，且肝脏FNDC5水平与肝脏脂肪变性和肝损伤程度呈正相关。Petta等[74]的研究也表明，NAFLD患者肝脏*FNDC5* mRNA水平与肝脏脂肪变性程度和纤维化程度相关，脂肪变性和纤维化程度更高的患者肝脏*FNDC5* mRNA表达更高。Zhu等[34]应用ELISA对肝脏Irisin水平进行检测，他们的结果显示，相较于正常饮食对照组，高脂饮食诱导的NAFLD小鼠肝脏Irisin水平显著升高。

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越来越多的证据表明，Irisin作为运动诱导的内分泌因子在调控肝脏脂质代谢改善NAFLD中起重要作用。但目前存在以下问题限制了Irisin的临床应用。a. 重组Irisin在体内的半衰期很短，不到1 h[12]。b. Irisin在NAFLD不同阶段可能发挥不同的作用：尽管大量的研究表明Irisin对NAFL和

NASH均有良好的改善作用，但Shi等[75]发现Irisin可通过激活PI3K-AKT通路增加肝细胞癌增殖和侵袭。c. Irisin干预可能导致一些副作用：Ho等[76]发现过量的Irisin会增加小鼠心脏氧化应激和细胞凋亡；Irisin还可能诱发性早熟[14, 77]；此外，Irisin具有增加能量消耗的作用，不当的应用可能会给慢性消耗性疾病带来不利的影响。因此，寻找延长Irisin半衰期的方法，明确Irisin对NAFLD不同阶段的作用，确定Irisin的适宜干预剂量和人群都极为重要。

关于Irisin在运动改善脂质代谢防治NAFLD中的作用尚存在许多需要进一步明确的问题。a. 现阶段对Irisin调控脂质代谢的研究多只检测脂质代谢相关蛋白，尚缺乏Irisin对肝脏脂质代谢率影响的直接证据，可利用荧光或放射性同位素示踪策略进一步明确Irisin对NAFLD脂质代谢的影响。b. *FNDC5*基因敲除实验可为“运动改善NAFLD是否依赖Irisin”这一问题提供关键证据，然而目前仍鲜见基因敲除动物在此方面的应用。c. NAFLD的发生发展机制复杂，涉及多组织器官的相互作用。除肌肉外，脂肪组织、肝脏、肾脏等均表达FNDC5，介导运动改善肝脏脂质代谢的Irisin是否主要来源于骨骼肌？其他组织器官在此过程中Irisin的产生和分泌有怎样的变化？各组织器官如何协同工作调控Irisin改善NAFLD脂质代谢？这些问题也需进一步探讨。明确上述问题有助于更好地理解Irisin介导运动在NAFLD等代谢疾病中的作用，进而为揭示运动防治NAFLD的机制、推动运动在改善NAFLD中的应用和寻找运动模拟药的可能靶点奠定基础。

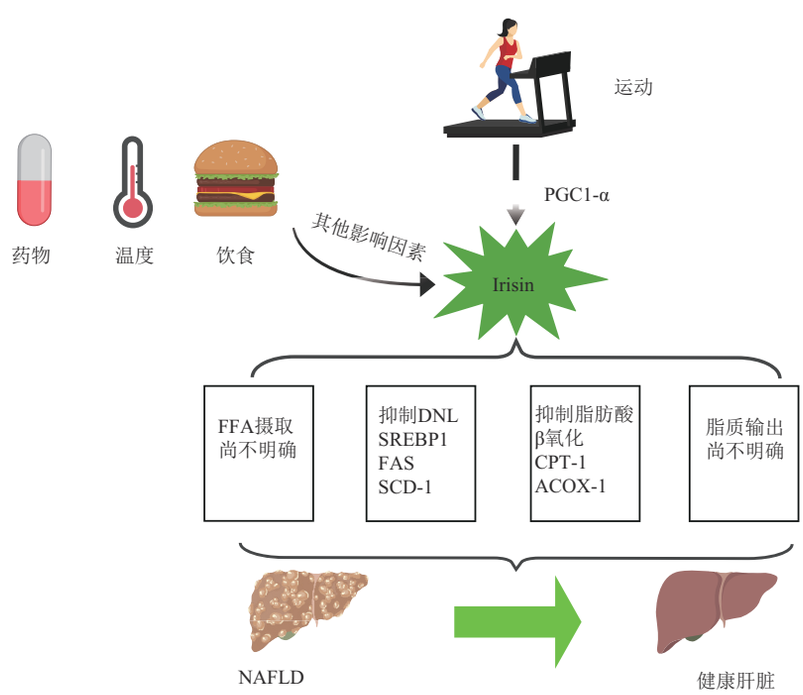

Fig. 2 Irisin improves liver lipid metabolism disorder and alleviates nonalcoholic fatty liver disease

图2 Irisin改善肝脏脂质代谢紊乱减轻非酒精性脂肪性肝病

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Research Status of Irisin in Improving Hepatic Lipid Metabolism Disorder and Reducing NAFLD*

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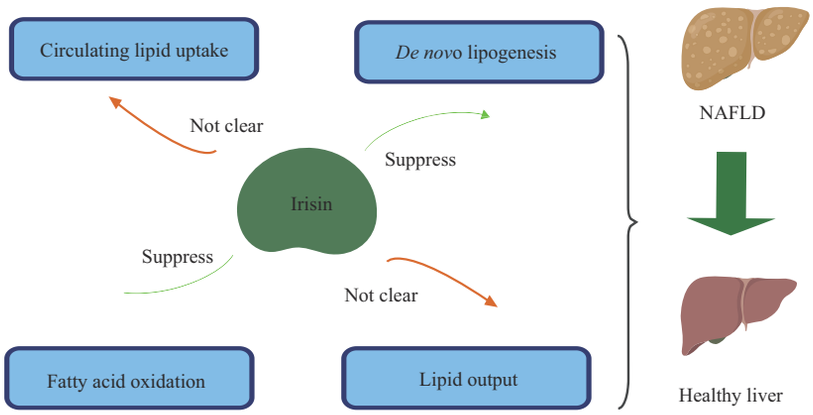
Graphical abstract



Abstract Nonalcoholic fatty liver disease (NAFLD) does great harm to human health, and the incidence is increasing year by year. The liver serves an important role in lipid metabolism. Hepatic steatosis develops as a consequence of lipid metabolic dysregulation, namely the imbalance among fatty acid uptake, *de novo* lipogenesis (DNL), fatty acid oxidation (FAO) and very low density lipoprotein-mediated lipid export. With diverse health-promoting effects, exercise is a cheap and effective intervention for the prevention and treatment of NAFLD. Amelioration of impaired lipid metabolism acts as an important mechanism by which exercise protects against NAFLD. However, how exercise ameliorates lipid metabolic dysregulation is still unclear. Skeletal muscle is not only a vital organ of motion, but also has an endocrine function, it secretes numerous myokines which mediates exercise-induced benefits on our body. Irisin is a small peptide derived from proteolytic cleavage of fibronectin type III domain containing protein 5 (FNDC5). As a myokine, its production is regulated by exercise and it play an important role in exercise-induced protection against obesity-related chronic diseases, such as NAFLD. A growing body of research has demonstrated that Irisin ameliorates lipid metabolic dysregulation in NAFLD. Irisin mediated inhibition of hepatic DNL and FAO has been reported. However, the effect of Irisin on fatty acid uptake and lipid export is still unknown. In the present review, we summarized the researches focusing on how exercise regulated Irisin production and the effect of Irisin on lipid metabolism on NAFLD. To clarify the above problems will help us to better understand the role of Irisin on exercise-mediated protection against NAFLD.

Key words Irisin, exercise, NAFLD, lipid metabolis

DOI：10.16476/j.pibb.2023.0359

* This work was supported by a grant from the Characteristic Innovation Program of Colleges and Universities in Guangdong Province (2021ZDZX2054).

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Received：September 13，2023 Accepted：March 15，2024