综述

运动调控JAK2/STAT信号通路治疗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)是现代社会中最常见的一类慢性肝病, 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。运动疗法作为一种最经济、便捷且有效的预防和治疗NAFLD的方式, 其机制涉及运动对于JAK2/STAT信号通路的调节。JAK2/STAT信号通路是一条与代谢相关的重要通路, 通路所涉及的JAK2及部分STAT分子活性水平的降低会导致肝脏细胞出现脂质沉积等不良反应, 阻碍肝脏脂质正常代谢, 从而引发NAFLD。该文梳理了前人的研究成果, 讨论运动通过调节机体内LEP、IGF-1、GH等的分泌水平, 直接或间接影响JAK2/STAT信号通路, 进而提升脂质代谢水平以改善NAFLD症状, 以期为运动干预治疗NAFLD机制探究提供参考。

关键词 非酒精性脂肪性肝病; 运动; JAK2; STAT

Research Progress on the Mechanism of Exercise Regulating JAK2/STAT Signaling Pathway to Treat the Non-Alcoholic Fatty Liver Disease

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Abstract NAFLD (non-alcoholic fatty liver disease) is the most common type of chronic liver disease in modern society, including non-alcoholic simple fatty liver disease and non-alcoholic steatohepatitis, which are often complicated by other metabolic disorders and seriously affect human health. Exercise therapy is the most economical, convenient and effective way to prevent and treat NAFLD, and its mechanism involves the regulation of JAK2/STAT signaling pathway, which is an important metabolism-related pathway. This paper discusses that exercise can directly or indirectly affect the JAK2/STAT signaling pathway by regulating the secretion levels of LEP, IGF-1 and GH in the body, which can enhance the level of lipid metabolism and improve NAFLD, in order to provide a reference for the mechanism of exercise intervention for NAFLD.

Keywords non-alcoholic fatty liver disease; exercise; JAK2; STAT

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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, 由药物、遗传疾病或其他相关肝损伤因素导致肝细胞脂肪变性和异常沉积的一类肝脏代谢性疾病[1-2], 其主要病理症状为肝细胞弥散性气泡样脂肪变性与三酰甘油蓄积等[3]。NALFD疾病谱包括非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), 且其在恶化过程中出现自发逆转的可能性较小(图1)[3-5]。由于NAFLD常伴有血脂异常、II型糖尿病、胰岛素拮抗等并发病症, 因此, NAFLD已被美国临床内分泌医学会列为代谢综合征的主要组成之一[6], 更有学者建议将NAFLD更名为代谢相关脂肪性肝病(metabolic associated fatty liver disease, MAFLD), 原因是MAFLD相比NAFLD更有利于临床诊断, 且有别于其他肝脏疾病[7]。然而目前临床上还没有治疗NAFLD的特效药, 治疗NAFLD的干预策略主要为饮食干预、手术干预及运动干预等[8], 与饮食干预、手术干预相比, 规律的运动干预治疗成本低且对患者身心有积极作用, 因此运动干预治疗NAFLD已成为运动科学与临床医学领域的研究热点之一。

NAFLD的治疗核心是改善患者的脂肪代谢情况。对于NAFLD患者而言, 长期的中高强度有氧运动有降低肝内甘油三脂含量的作用, 可以显著降低患者的体重、体脂含量、血压等指标[9]。在一项研究中发现, 长期运动干预后即使NAFLD患者体重指标变化不明显, 肝脏脂质也可以相对减少13%[10]。低成本的运动干预可有效地防治NAFLD患者脂肪代谢, 减少肝脏脂质蓄积, 对于NAFLD治疗有着积极作用。运动干预治疗NAFLD过程中, Janus激酶2/信号转导与转录激活因子(the Janus kinase/signal transducer and activator of transcription, JAK2/STAT)信号通路具有重要作用: 运动通过调控JAK2/STAT信号通路表达水平, 靶向作用患病个体肝脏脂质沉积、脂肪变性、炎症反应等情况以实现症状改善。因此明确运动如何调控该信号通路显得十分重要[11]。进一步研究发现, 运动对瘦素(leptin, LEP)、生长激素(growth hormone, GH)、胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)、白细胞介素-22(interleukin-22, IL-22)的分泌起到调控作用[12-14], 而这几种因子的分泌水平在激活与调控JAK2/STAT信号通路中起到重要作用[15-17], 故了解运动靶向干预LEP、GH等因子分泌以激活与调控JAK2/STAT信号通路的机制可为缓解NAFLD和开发新的治疗策略提供重要信息与线索。近年来, 聚焦在通过干预JAK2/STAT信号通路表达治疗NAFLD的研究越来越多, 但对运动调控该信号通路治疗NAFLD的研究还存在一定不足。因此, 本文综述了运动干预LEP、GH、IGF-1、IL-22的分泌水平以激活与调控JAK2/STAT信号通路, 并调节相关下游因子分泌以治疗NAFLD的机制, 以期推动运动手段治疗NAFLD的研究。

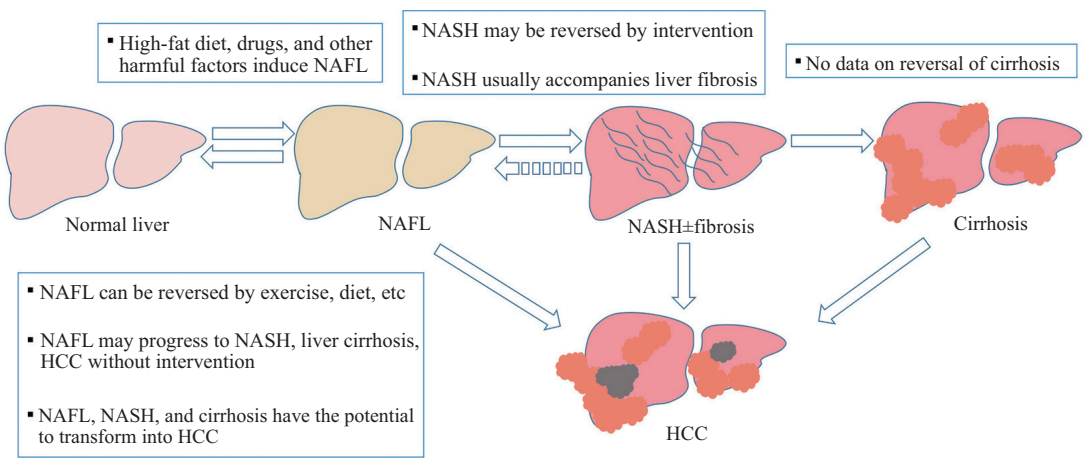

图1 NAFLD的病变发展(根据参考文献[3-5]修改)

Fig.1 Development of NAFLD (modified from the references [3-5])

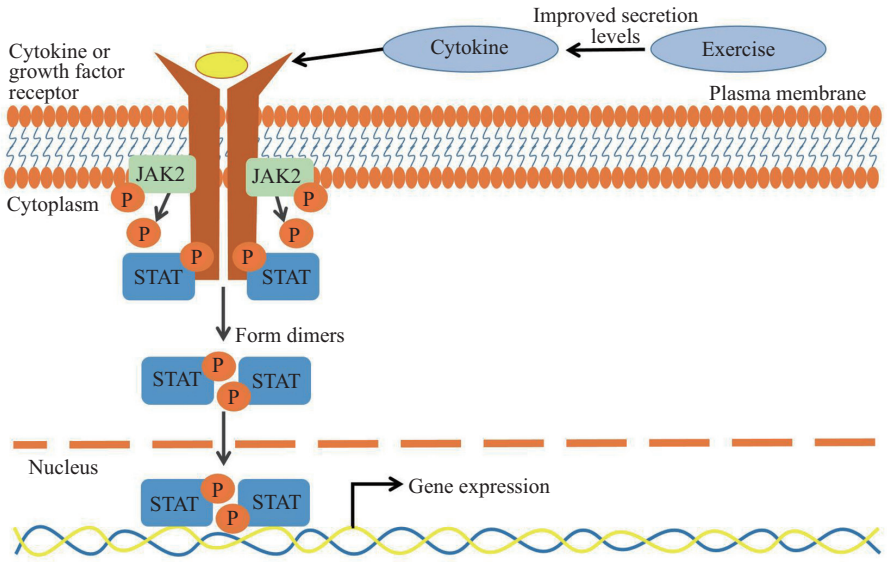

图2 JAK2/STAT信号通路传递过程(根据参考文献[12]修改)

Fig.2 JAK2/STAT signaling pathway transmission process (modified from the reference [12])

1 JAK2/STAT信号通路与NAFLD

JAK2是JAK家族中普遍表达的成员，可被肝脏中多种细胞因子包括GH、LEP和白细胞介素-6(interleukin-6, IL-6)等激活[18]。JAK2的信号通过STAT转导，介导与细胞增殖和存活相关的基因转录与表达，对炎症和肿瘤发展具有密切相关的作用[19]。STAT家族不同成员的表达量对于NAFLD作用不同，如STA4T1、STAT4的高表达会促进肝脏细胞脂肪变性[20-21]；STAT3在促进LC发病进程中起抗炎或促炎作用[19,22]；STAT5、STAT6的高表达可以有效预防NAFLD恶化[23-24]。运动干预可抑制STAT1等不利STAT并促进STAT5等有益STAT的表达[23,25]，后文JAK2/STAT信号通路中的STAT主要指有益STAT。

JAK2/STAT信号通路的基本传递过程是：细胞因子与细胞膜上受体特异性结合后激活JAK2，活化的JAK2催化受体本身的酪氨酸磷酸化并招募STAT，STAT在JAK2的作用下实现其磷酸化活化，然后STAT形成同源或异源二聚体并入核，与DNA上的反应元件结合进而实现对靶基因的调控(图2)[18]。

JAK2/STAT信号通路是多种细胞因子和生长因子在细胞内传递信号的共同途径，介导细胞增殖、分化、凋亡等过程，对于个体的生长与稳态维持必不可少[19]。有研究显示肝细胞特异性缺失JAK2的小鼠会自发出现NAFLD，无独有偶，人类的JAK2/STAT信号通路受到破坏也会引发肝脏脂质代谢困难，进而出现NAFLD[16,26]。上述结果表明，在肝脏中JAK2/STAT信号通路的异常与NAFLD的发生发展密切相关。抑制LEP分泌，促进GH、IGF-1和IL-22分泌均可调控JAK2/STAT信号通路[27-30]，起到改善NAFLD症状的作用，但不同STAT表达对于NAFLD的作用不同：有研究显示肝脏细胞氧化应激会增强STAT1、STAT3的信号转导作用，加速肝脏炎症与癌变[31]，但MILLER等[32]发现STAT3的高表达对于白细胞介素-10(interleukin-10, IL-10，一种关键的抗炎因子)缺失个体的肝脏抗炎与脂肪变性是有益的。

2 运动调控JAK2/STAT信号通路治疗NAFLD

目前能有效减少肝脏脂肪的运动类型主要包括有氧运动、阻抗运动及高强度间歇运动等。有氧运动可以通过激活脂肪分解，缓解肝脏脂肪沉积，以达到防治NAFLD的目的。中高强度的有氧运动可有效降低患者体重与肝脏内甘油三酯含量，有助于改善NAFLD患者的肝脏脂肪堆积[9]。阻抗运动指的是肌肉在克服外来或者自身阻力的主动运动，其被视为治疗NAFLD的补充手段，原因是阻抗运动对于人体心肺功能要求更低且有助于患者肌肉增长[33]。随着肌肉含量的增加，机体总肌肉代谢上升，同时体脂总量下降，而在进行阻抗运动后，其基础代谢延长

效果可以使NAFLD患者增大能量消耗, 减少肝脏脂肪生成量。高强度间歇运动可以减少肝脏脂肪沉积和改善胆固醇指标[34], 降低患者的运动不适感, 增加运动愉悦性, 这是高强度间歇运动的独特优势。虽然三种运动均可起到降低肝内脂质含量的作用, 但SECHANG等[35]发现高强度间歇运动通过调节体内脂肪酸代谢与肥胖相关炎症的方式, 可以有效改善LC与恢复Kupffer细胞的吞噬能力, 这是高强度间歇运动所独有的。有氧运动、阻抗运动、高强度间歇运动项目可靶向作用于肝细胞脂代谢调节、炎症反应、氧化应激、细胞凋亡等, 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[36]。合适的运动剂量与方案制定还需要更深入的研究, 包括最佳体力活动频率、持续时间或强度, 但可以肯定的是, 一定强度的运动对于肝脏表现是有益的[9], 因此运动干预可以成为治疗NAFLD方法中的一部分。

JAK2/STAT信号通路中断或者受抑制使得肝脏脂质积累, 加重细胞的氧化应激与炎症反应, 引发肝细胞脂肪变性, 进而诱发NAFLD[37-38]。而运动可调控个体JAK2/STAT信号通路表达水平, 靶向作用于肝脏脂质代谢、脂肪变性、炎症反应等, 以改善NAFLD症状。在运动调控JAK2/STAT信号通路表达治疗NAFLD的机制中, LEP、IGF-1、GH、IL-22起到重要作用。

2.1 LEP在运动调控JAK2/STAT信号通路的作用

LEP主要由白色脂肪组织分泌, 与位于下丘脑神经元的受体结合, 通过激活下游信号通路, 发挥抑制食欲、增加能量消耗、改善糖脂代谢等作用, 但过高的LEP水平会加速NAFLD的病程发展[39]。LEP的生理功能需要由JAK2/STAT信号通路进行转导才能实现。莫灿婷等[27]发现, 通过针刺手段可使肥胖小鼠LEP分泌减少, 有效提升STAT5表达水平及JAK2/STAT信号通路活性水平, 这对于治疗NAFLD有重要意义, 但LEP缺失的小鼠会出现严重的肝脏脂肪变性, STAT的表达明显降低, 后续也会诱发NASH[40]。

NAFLD个体常出现高水平LEP分泌与抵抗的情况, 且同NAFLD严重程度呈正相关, 而运动可通过抑制LEP高水平分泌与LEP抵抗, 有效改善NAFLD症状[12,41]。肥胖大鼠在运动后血清LEP水平下降且胰岛素抵抗现象有所改善, 推测LEP与胰岛素之间存在一定的潜在关系, 通过药物干预和基因敲除技术证明其中的桥梁是JAK2/STAT信号通路[42]。肥胖大鼠出现高水平LEP分泌与LEP抵抗后, 这会导致JAK2/STAT表达水平减弱, 而通过运动可有效逆转LEP抵抗并降低LEP分泌水平, 实现上调JAK2/STAT信号通路活性的同时提高通路下游蛋白激酶B(protein kinase B, PKB)的表达水平[43]。长期进行慢性有氧运动的小鼠与久坐小鼠相比, 前者对LEP的敏感性有一定程度提升, 其体内JAK2磷酸化水平增加[44], 进一步激活个体的JAK2/STAT信号通路, 导致运动小鼠患NAFLD的几率明显降低。以上结果提示, 运动可以有效抑制NAFLD个体的LEP高水平分泌, 改善LEP与胰岛素的抵抗现象, 进而介导JAK2/STAT信号通路表达水平上升, 促进NAFLD个体的脂质代谢, 有利于患病个体代谢稳态的维持与体重减轻, 对于NAFLD防治有着重要作用。

2.2 IGF-1在运动调控JAK2/STAT信号通路的作用

IGF-1是一种在分子结构上与胰岛素类似的多肽类物质, 肝脏作为IGF-1分泌的主要器官, 其生理功能同时也受IGF-1的调控。IGF-1与相关受体结合后可起到增强肝脏细胞的抗氧化应激、抗细胞凋亡等作用[13,45]。研究表明, 如果人体内的IGF-1循环水平过低会引发慢性肝病, 其中包括NAFLD和LC[46]。通过小鼠实验与体外细胞实验发现, IGF-1会上调JAK2/STAT信号通路的表达水平, 从而起到改善脂质代谢的作用; 如果IGF-1受体缺失或被抑制, 则会抑制JAK2/STAT信号通路活性[29,47], 个体脂质代谢也因此受阻, 从而诱发NAFLD。

作为提升内源性IGF-1水平的手段之一, 在运动干预后机体内IGF-1循环水平提升, 可以有效缓解NAFLD[13]。长期有氧运动与阻抗运动均可以起到调控个体IGF-1循环水平的作用, 减少NAFLD患者肝脏脂质含量[48]。大鼠在经过长期的有氧运动后, 体内的IGF-1水平明显上升同时抑制了LEP的分泌, 有效预防了NAFLD及LC的发生[49]。由上述可知, IGF-1的表达水平与JAK2/STAT的通路活性是密切相关的, 两者对于机体脂质代谢具有重要作用。IGF-1在肝脏脂肪代谢、氧化应激中扮演重要角色, 作为NAFLD预测与诊断的关键指标具有参考意义, 这也提示我们IGF-1或许是NAFLD的治疗靶点。运动干预可有效提升IGF-1循环水平, 上调JAK2/STAT信号通路表达水平, 抑制NAFLD的病情发展。在肝

脏中IGF-1还与GH起到协同作用, 共同介导JAK2/STAT信号通路表达水平的提升, 这对于代谢疾病有着重要启示作用[50], 将在后文进行阐述。

2.3 GH在运动调控JAK2/STAT信号通路的作用

GH是一种分子质量为22 kDa, 含191个氨基酸残基的单链多肽类激素。诸多研究已证实GH缺乏与NAFLD发生存在密切关系: 垂体功能减退的患者NAFLD发生率会明显高于正常人, 而对患者进行GH补充可以有效地改善患者血清转氨酶水平, 甚至逆转NAFLD[51-53], 这提示GH不足可能是导致患NAFLD的主要因素。GH受体(growth hormone receptor, *GHR*)基因缺陷的小鼠会出现肝脏脂质含量增加、胰岛素抵抗等, 表现出NAFLD症状[54], 但是有效的GH治疗可以改善小鼠中的血清转氨酶水平及肝脏形态学变化[55], 以上结果表明GH在防治肝脏脂肪变性方面尤为重要。GH通过血液循环作用于位于肝脏细胞的GHR, 两者直接相互作用或者通过IGF-1进行间接介导, 可以同时激活GHR与JAK2磷酸化形成GH-GHR-JAK2多聚体, 随后激活JAK2/STAT信号通路, 其中STAT被视为GH信号介导的介质[16,28]。肝细胞中STAT表达水平较高, 且会影响GH诱导基因的表达: STAT可以通过调节IGF-1水平来控制全身GH水平和限制GH诱导基因的表达, 从而影响肝脏脂质分解[56]。虽然GH/JAK2/STAT信号转导在患者肝脏代谢中的机制仍不完全清楚, 但是已有研究表明肝脏GH/JAK2/STAT信号转导的缺失会造成肝脏脂肪变性[16,37], 可以肯定的是肝脏内JAK2/STAT通路信号转导的损害与葡萄糖异常代谢、脂肪肝疾病及炎症发生存在关联。此外, 运动存在促进GH水平上升的功能, 且与IGF-1的表达存在一定的关系: 运动后IGF-1表达水平也因GH水平升高而升高[57], 这可能也和两者的协同作用有关。

运动引起内脏脂肪降低是多方面因素综合作用的结果, 其中包括运动引起GH升高的因素[14]。较高强度的运动会使GH水平上升, 这或许与GH可以加强运动适应有关[58]。运动诱导GH的分泌水平上升的同时, 也能起到加快运动后脂肪分解的速度[59]。对比人类在短期的阻抗运动、急性运动、耐力运动之后的激素反应, 结果显示对于GH均有提升作用, 但阻抗运动效果相对较差[60], 说明GH分泌水平是受运动类型影响的。短期运动干预会让GH水平上升, 长期运动干预也有相同的效果。在一项长达10周的有氧运动干预研究中, 发现受试者血液中胆固醇水平有效改善的同时, GH水平也出现显著上升[61]。以上研究提示, 运动可以有效提升GH的分泌水平, 促进内脏脂肪组织分解, 达到改善NAFLD的目的, 这对于治疗NAFLD有重要意义。综上所述, 正常的GH分泌可以促进个体生长发育和正常代谢的运行, 如果缺乏足够的GH, 会造成个体发育迟缓和代谢障碍, 同时肝脏中的能量代谢负担也会加重, 并且容易造成肝脏脂肪变性形成NAFLD。运动提高GH的分泌水平, 可有效地改善代谢相关的问题。在JAK2/STAT信号通路正常的情况下, GH分泌上升可以激活该通路, 并且该通路也会调节GH分泌, 达到适宜稳态, 以保证肝脏糖代谢、脂肪代谢的正常进行, 从而达到改善或者预防NAFLD症状的作用。

2.4 IL-22在运动调控JAK2/STAT信号通路的作用

白细胞介素-22(interleukin-22, IL-22)是IL-10家族成员, 在控制炎症与肝脏再生中起着重要作用, 同时也与肝脏纤维化有着重要关系[62]。IL-22在某些研究中被视为抑制肝脏病变的关键, 可以有效修复肝脏组织[63-64]。IL-22能靶向激活肝脏STAT信号转导及调节脂质代谢基因表达, 有效减轻肝脏脂肪变性, 从而改善NAFLD症状[65-66]。在动物实验中, IL-22的缺失会导致小鼠肝损伤从而引发NAFLD[67], 而补充外源性的IL-22可以改善NAFLD小鼠的症状[68]。IL-22在减轻肝脏脂肪变性的同时, 对于肝脏的抗纤维化也有一定作用[69]。当肝脏出现炎症时, IL-22表达水平上升并通过STAT3促进肝脏干/祖细胞(liver stem/progenitor cells, LPCs)增殖[30], 旨在实现修复受损肝组织, 这对于改善NAFLD症状有一定意义。现关于IL-22的研究中, 暂无数据说明运动可以直接促进IL-22分泌, 但有研究指出不同强度的运动会对个体IL-22体循环浓度产生影响[70]。综上所述, 推测运动可以影响IL-22分泌水平, 以提升JAK2/STAT信号通路表达, 缓解NAFLD症状。

2.5 运动干预对通路下游因子的调控

多种强度与类型的运动会影响LEP、IGF-1、GH、IL-22的分泌, 以促进JAK2/STAT信号通路活性水平的提高, 并调节如PKB、IL-6等下游因子分泌水平(表1), 以改善或预防肝脏脂质代谢、氧化应激、炎症反应等情况。

JAK2/STAT信号通路中和肝脏脂肪分解、合成、代谢相关的下游因子有脂肪甘油三脂脂肪酶(adi-

pose triglyceride lipase, ATGL)、脂肪酸合成酶(fatty acid synthase, FAS)、成纤维细胞生长因子21(fibroblast growth factor 21, FGF21)。ATGL是一种富含脂肪的蛋白质, 在机体内起到催化分解脂肪组织甘油三酯的作用, 其表达受LEP水平及JAK2/STAT信号通路活性水平影响, 是该通路的下游分子[71]。有研究证明, 在运动后, ATGL上升可以上调PKB水平, 加速脂肪代谢[72]。有氧运动通过促进ATGL表达, 可以减轻炎症并改善肝脏脂肪变性[73]。FAS是人体脂肪酸形成的关键酶之一, 促进脂质合成, 是受JAK2/STAT信号通路影响的下游因子之一。抑制FAS表达可以有效抑制脂肪沉积并分解肝脏脂肪[74]; JAK2/STAT信号通路缺失的小鼠体内FAS水平升高, 加速脂肪肝的形成[75]; 而该通路的激活会使FAS表达水平降低, 改善肝脏炎症, 减少肝脏脂质沉积[76]。同时FAS分泌水平还受ATGL、PKB影响, FAS与ATGL、PKB呈负相关关系[77-78]。上述内容提示在运动干预后, JAK2/STAT信号通路通过直接或者间接的方式对FAS进行调节, 进一步抑制个体脂质沉积, 改善NAFLD症状。FGF21是主要由肝脏分泌的生长因子, 在肝脂代谢过程中发挥重要作用, 对NAFLD有抑制与改善作用[20,79]。研究表明, GH可以刺激FGF21表达[80]; GH/JAK2/STAT信号转导被抑制后, 下游FGF21表达受阻[29]; 个体在运动后肝脏内的FGF21表达水平显著升高, 肝脏脂质变性情况得到改善, 有效抑制肝脏细胞脂质蓄积, 缓解NAFLD的病情发展[81]。目前关于FGF21与JAK2/STAT信号通路的研究尚存空缺, 但综上可知, 作为GH的下游因子, GH上调JAK2/STAT信号通路表达, 同时FGF21分子水平升高, 提升个体的糖脂代谢水平, 改善NAFLD症状。

JAK2/STAT信号通路中同肝脏抑制细胞凋亡、氧化应激、炎症相关的下游因子有PKB、核因子E2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)、IL-6。PKB及蛋白激酶B/糖原合成酶激酶-3β(PKB/GSK3β)信号通路表达在抑制肝脏细胞凋亡与炎症反应中有着重要作用: NAFLD个体肝脏PKB表达水平相对较低, 经过运动干预后, PKB浓度呈现上升趋势[82-84], PKB/GSK3β信号通路表达水平上升, 并抑制caspase-3(肝脏内的促凋亡因子, 肝细胞凋亡随caspase-3表达水平的增高而增加)的活性, 以起到抑制肝细胞凋亡作用。目前对于JAK2/STAT信号通路下游PKB之间的机制关系了解尚少, 但是可以推测的是, 运动可以通过提高JAK2/STAT信号通路水平, 从而调控下游的PKB蛋白, 以提升NAFLD个体的肝细胞抗凋亡能力, 从而实现逆转NAFLD。Nrf2是调节抗氧化应激反应的重要转录因子, 几乎存在于所有细胞中, 在肝脏中表达较高, 被认为是治疗NAFLD的新靶点[85-86]。Nrf2缺失的个体会出现NAFLD并且快速发展为NASH, NAFLD个体的Nrf2表达水平也较低, 而通过运动干预, 可以有效提升肝脏内的Nrf2水平[87-88]。目前Nrf2与JAK2/STAT通路的研究还不够深入, 但可以推测, 运动通过提升JAK2/STAT信号通路表达水平的方式, 上调下游Nrf2蛋白的水平, 以提升NAFLD个体的肝脏抗氧化应激能力, 达到改善症状的目的。IL-6是LEP的下游

表1 不同类型运动调节JAK2/STAT信号通路相关因子的分泌

Table 1 Different exercise regulate the secretion of factors related to the JAK2/STAT signaling pathway

研究对象 Object of study	运动周期/运动类型 Cycle and type of exercise	研究结果 Result
NAFLD patient	12-week resistant exercise	Declining LEP level[41]
NAFLD patient	16-week aerobic combined with resistance exercise	Declining LEP level and rising IGF-1 level[48]
Obese rat	8-month aerobic exercise	Declining LEP level and rising IGF-1 level[49]
Obese patient	12-week aerobic combined with resistance exercise	Rising IGF-1 and GH level[93]
Obese patient	12-week high-intensity interval exercise	Rising GH level[94]
Obese patient	16-week high-intensity interval exercise	Rising IL-22 level[70]
Obese mice	8-week aerobic exercise	Rising PKB level and declining FAS level[83]
Obese patient	Long-term moderate intensity aerobic exercise	Rising GH and FGF21 level, and declining IL-6 level[95]
NAFLD mice	8-week aerobic exercise	Declining IL-6 level [96]
NAFLD zebrafish	12-week aerobic exercise	Rising Nrf2 level[87]
Obese mice	8-week aerobic exercise	Rising ATGL level and declining IL-6 level[73]

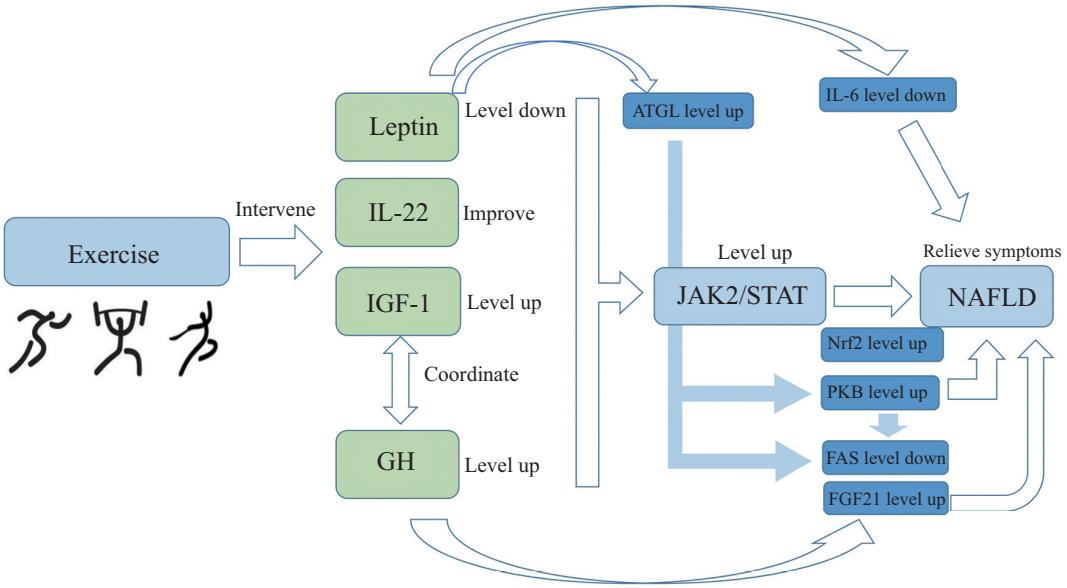

图3　运动调控JAK2/STAT信号通路改善NAFLD机制示意图

Fig.3　Schematic diagram of the mechanism by which exercise modulates the JAK2/STAT signaling pathway to improve NAFLD

分子，高水平IL-6可以利用JAK2/STAT信号通路介导炎症因子进一步释放[89]，对NAFLD的炎症发展有促进作用。运动和其他因素降低NAFLD个体LEP水平的同时使得IL-6水平降低[90-91]。提示IL-6分泌减少是通过LEP水平下降来实现的，进而影响JAK2/STAT信号通路，起到改善脂质代谢与抗炎的作用。不过也有研究表示，运动可能是直接调节IL-6分泌，从而影响JAK2/STAT通路的[92]。

以上数据表明，运动对于LEP、GH、IGF-1、IL-22等及下游因子具有调控作用，能够借此调节JAK2和STAT蛋白的表达水平，达到直接或间接改善NAFLD症状的作用(图3)。

3　总结与展望

NAFLD对于人类健康生活有着不可忽视的影响，在目前乃至未来很长一段时间仍是需要被高度重视的一种代谢疾病。目前学界对于运用运动手段干预NAFLD是持肯定态度的，其通过减少个体体重的方式来改善NAFLD症状个体的肝脏表现，即使运动没有减轻患者体重，也能降低患NAFLD的风险。但是其中关于运动的重要因素如方式、强度、时间等，需要有更加深层次的研究才能确定。现有研究已证明在运动干预治疗NAFLD过程中JAK2/STAT信号通路表达水平会明显上升，这提示我们运动治疗NAFLD必然和该信号通路存在一定联系。在运动调控JAK2/STAT信号通路治疗NAFLD的机制中LEP、IGF-1、GH、IL-22或许是其中的关键：LEP的过度表达会抑制JAK2/STAT信号通路并影响代谢，运动可以改善个体对于LEP的敏感性并抑制其高水平分泌，从而提升通路表达水平以缓解NAFLD症状，但需要强调的是LEP的缺失也会导致NAFLD诱发；运动在刺激机体产生IGF-1的同时，也进一步促进JAK2/STAT信号通路表达，这提示我们运动可通过与IGF-1关联的JAK2/STAT信号通路表达，以起到改善NAFLD症状的作用；GH/JAK2/STAT通路受损或者缺失都会对肝脏脂质代谢产生影响，在JAK2/STAT信号通路正常的情况下，运动可以改善GH分泌水平，从而使得NAFLD患者的JAK2/STAT信号通路表达水平上升，促进肝脏脂质代谢，达到改善NAFLD症状的目的；目前尚无直接数据证明运动刺激IL-22分泌，但是作为JAK2/STAT信号通路的相关因子，可以推测两者存在一定的联系；运动促进JAK2/STAT信号通路表达，调控PKB、Nrf2、ATGL、FAS等下游因子的表达水平，以提升患病个体的肝脏细胞抗凋亡、抗氧化应激、脂质代谢能力，从而达到防治NAFLD的效果。

目前学术界对于运动改善NAFLD症状的通路机制研究尚不完全明确，但尝试从JAK2/STAT这条与代谢相关的通路去理解或许将会有新的发现。当前暂无实际研究可以直接证明运动可以对JAK2/STAT

通路中断或受抑制个体实现NAFLD病症改善, 对此还需进行更为深入的研究。LEP、IGF-1和GH在肝脏研究中作为常被关注的要素, 或许随着研究的深入, 对于这三者在NAFLD的运动疗法中的作用与地位会有新的理解。此外, 与JAK2/STAT信号通路相关的下游蛋白也将会是未来的研究重点。最新研究显示, 肝脏中的特异性miRNA对于肝脏脂质代谢与炎症反应有着重要作用, 运动可以通过调控miRNA表达来改善NAFLD病症, 这或许也是运动手段治疗NAFLD的机制之一[97]。因此, 就运动防治NAFLD的具体作用机制来说, 还需要更多的深入研究。

参考文献 (References)

[1] NASSIR F. NAFLD: mechanisms, treatments, and biomarkers [J]. Biomolecules, 2022, 12(6): 824.

[2] SCORLETTI E, CARR R M M. A new perspective on NAFLD: focusing on lipid droplets [J]. J Hepatol, 2022, 76(4): 934-45.

[3] SCHUSTER S, CABRERA D, ARRESE M, et al. Triggering and resolution of inflammation in NASH [J]. Nat Rev Gastroenterol Hepatol, 2018, 15(6): 349-64.

[4] FRIEDMAN S L, NEUSCHWANDER-TETRI B A, RINELLA M, et al. Mechanisms of NAFLD development and therapeutic strategies [J]. Nat Med, 2018, 24(7): 908-22.

[5] FAN J G, KIM S U, WONG V W S. New trends on obesity and NAFLD in Asia [J]. J Hepatol, 2017, 67(4): 862-73.

[6] GARVEY W T, MECHANICK J I, BRETT E M, et al. American association of clinical endocrinologists and American college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity [J]. Endocr Pract, 2016, 22: 1-203.

[7] ESLAM M, SANYAL A J, GEORGE J, et al. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease [J]. Gastroenterology, 2020, 158(7): 1999-2014.

[8] SAMUEL V T, SHULMAN G I. Nonalcoholic fatty liver disease as a nexus of metabolic and hepatic diseases [J]. Cell Metab, 2018, 27(1): 22-41.

[9] ZHANG H J, HE J, PAN L L, et al. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: a randomized clinical trial [J]. JAMA Intern Med, 2016, 176(8): 1074-82.

[10] HALLSWORTH K, FATTAKHOVA G, HOLLINGSWORTH K G, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss [J]. Gut, 2011, 60(9): 1278-83.

[11] SHI S Y, LUK C T, SCHROER S A, et al. Janus Kinase 2 (JAK2) dissociates hepatosteatosis from hepatocellular carcinoma in mice [J]. J Biol Chem, 2017, 292(9): 3789-99.

[12] OBRADOVIC M, SUDAR-MILOVANOVIC E, SOSKIC S, et al. Leptin and obesity: role and clinical implication [J]. Front Endocrinol, 2021, 12: 585887.

[13] 李博文, 冯丽丽, 田振军. 胰岛素样生长因子-1与代谢性疾病及运动干预的研究进展[J]. 生理学报(LI B W, FENG L L, TIAN Z J. Advances in research on insulin-like growth factor-1 and metabolic diseases and exercise intervention [J] Shen Li Xue Bao), 2021, 73(2): 342-52.

[14] SABAG A, CHANG D, JOHNSON N A. Growth hormone as a potential mediator of aerobic exercise-induced reductions in visceral adipose tissue [J]. Front Physiol, 2021, 12: 623570.

[15] LI J, CHOI E, YU H, et al. Structural basis of the activation of type 1 insulin-like growth factor receptor [J]. Nat Commun, 2019, 10(1): 4567.

[16] KALTENECKER D, THEMANNS M, MUELLER K M, et al. Hepatic growth hormone-JAK2-STAT5 signalling: metabolic function, non-alcoholic fatty liver disease and hepatocellular carcinoma progression [J]. Cytokine, 2019, 124: 154569.

[17] LI S, LI X. Leptin in normal physiology and leptin resistance [J]. Sci Bull, 2016, 61(19): 1480-8.

[18] DODINGTON D W, DESAI H R, WOO M. JAK/STAT-emerging players in metabolism [J]. Trends Endocrinol Metab, 2018, 29(1): 55-65.

[19] RAH B, RATHER R A, BHAT G R, et al. JAK/STAT signaling: molecular targets, therapeutic opportunities, and limitations of targeted inhibitions in solid malignancies [J]. Front Pharmacol, 2022, 13: 821344.

[20] SAHINI N, BORLAK J. Genomics of human fatty liver disease reveal mechanistically linked lipid droplet-associated gene regulations in bland steatosis and nonalcoholic steatohepatitis [J]. Transl Res, 2016, 177: 41-69.

[21] MARTI-RODRIGO A, ALEGRE F, MORAGREGA A B, et al. Rilpivirine attenuates liver fibrosis through selective STAT1-mediated apoptosis in hepatic stellate cells [J]. Gut, 2020, 69(5): 920-32.

[22] ZHAO J, QI Y F, YU Y R. STAT3: a key regulator in liver fibrosis [J]. Ann Hepatol, 2021, 21: 100224.

[23] 张树玲, 李军汉, 王佳倩, 等. 有氧运动干预非酒精性脂肪肝小鼠肝脏JAK2/STAT5信号通路的变化[J]. 中国组织工程研究(ZHANG S L, LI J H, WANG J Q, et al. Aerobic exercise intervenes in the hepatic JAK2/STAT5 signaling pathway in mice with non-alcoholic fatty liver disease [J]. Chin J Tissue Eng Res), 2022, 26(17): 2690-5.

[24] 郝明月, 孙琳琳, 盛明薇, 等. 小檗碱对小鼠非酒精性脂肪性肝病程序性坏死的影响及其与AMPK/STAT6通路的关系[J]. 中华内分泌代谢杂志(HAO M Y, SUN L L, SHENG M W, et al. Effect of berberine on programmed necrosis in mice with non-alcoholic fatty liver disease and its relationship with AMPK/STAT6 pathway [J]. Chin J Eodocrinol Metab), 2022, 38(3): 225-30.

[25] CHEN Z, LI B, ZHAN R Z, et al. Exercise mimetics and JAK inhibition attenuate IFN-gamma-induced wasting in engineered human skeletal muscle [J]. Sci Adv, 2021, 7(4): eabd9502.

[26] SOS B C, HARRIS C, NORDSTROM S M, et al. Abrogation of growth hormone secretion rescues fatty liver in mice with hepatocyte-specific deletion of JAK2 [J]. J Clin Invest, 2011, 121(4): 1412-23.

[27] 莫灿婷, 唐红珍, 谢汉兴, 等. 针刺对肥胖大鼠下丘脑Leptin/JAK2/STAT5信号通路的影响[J]. 中华中医药杂志(MO C T, TANG H Z, XIE H X, et al. Effect of acupuncture on the Leptin/JAK2/STAT5 signaling pathway in the hypothalamus of obese rats [J]. China J Tradit Chin Med Pharm), 2022, 37(7): 4070-3.

[28] HU B, LI H, ZHANG X. A balanced act: the effects of GH-GHR-

IGF1 axis on mitochondrial function [J]. Front Cell Dev Biol, 2021, 9: 630248.
[29] XIA W, WANG Y, ZHANG Y, et al. Endoplasmic reticulum stress induces growth retardation by inhibiting growth hormone IGF-I axis [J]. Growth Horm IGF Res, 2020, 55: 101341.
[30] FENG D, KONG X, WENG H, et al. Interleukin-22 promotes proliferation of liver stem/progenitor cells in mice and patients with chronic hepatitis B virus infection [J]. Gastroenterology, 2012, 143(1): 188-98.
[31] GROHMANN M, WIEDE F, DODD G T, et al. Obesity Drives STAT-1-dependent NASH and STAT-3-dependent HCC [J]. Cell, 2018, 175(5): 1289-306.
[32] MILLER A M, WANG H, BERTOLA A, et al. Inflammation-associated interleukin-6/signal transducer and activator of transcription 3 activation ameliorates alcoholic and nonalcoholic fatty liver diseases in interleukin-10-deficient mice [J]. Hepatology, 2011, 54(3): 846-56.
[33] HASHIDA R, KAWAGUCHI T, BEKKI M, et al. Aerobic vs resistance exercise in non-alcoholic fatty liver disease: a systematic review [J]. J Hepatol, 2017, 66(1): 142-52.
[34] SABAG A, BARR L, ARMOUR M, et al. The effect of high-intensity interval training vs moderate-intensity continuous training on liver fat: a systematic review and meta-analysis [J]. J Clin Endocrinol Metab, 2022, 107(3): 862-81.
[35] SECHANG O, RINA S, TAKASHI S, et al. High-intensity aerobic exercise improves both hepatic fat content and stiffness in sedentary obese men with nonalcoholic fatty liver disease [J]. Sci Rep, 2017, 7: 43029.
[36] ZHOU B J, HUANG G, WANG W, et al. Intervention effects of four exercise modalities on nonalcoholic fatty liver disease: a systematic review and Bayesian network meta-analysis [J]. Eur Rev Med Pharmacol Sci, 2021, 25(24): 7687-97.
[37] THEMANNS M, MUELLER K M, KESSLER S M, et al. Hepatic deletion of Janus Kinase 2 counteracts oxidative stress in mice [J]. Sci Rep, 2016, 6: 34719.
[38] ZHANG Y, WANG S, ZHAO T, et al. Mono-2-ethylhexyl phthalate (MEHP) promoted lipid accumulation via JAK2/STAT5 and aggravated oxidative stress in BRL-3A cells [J]. Ecotoxicol Environ Saf, 2019, 184: 109611.
[39] MARQUES V, AFONSO M B, BIERIG N, et al. Adiponectin, Leptin, and IGF-1 are useful diagnostic and stratification biomarkers of NAFLD [J]. Front Med, 2021, 8: 683250.
[40] IMAJO K, FUJITA K, YONEDA M, et al. Hyperresponsivity to low-dose endotoxin during progression to nonalcoholic steatohepatitis is regulated by leptin-mediated signaling [J]. Cell Metab, 2012, 16(1): 44-54.
[41] OH S, SO R, SHIDA T, et al. High-intensity aerobic exercise improves both hepatic fat content and stiffness in sedentary obese men with nonalcoholic fatty liver disease [J]. Sci Rep, 2017, 7: 43029.
[42] ZHENG X, NIU S. Leptin-induced basal Akt phosphorylation and its implication in exercise-mediated improvement of insulin sensitivity [J]. Biochem Biophys Res Commun, 2018, 496(1): 37-43.
[43] ODERMATT T S, DEDUAL M A, BORSIGOVA M, et al. Adipocyte-specific gp130 signalling mediates exercise-induced weight reduction [J]. Intl J Obes, 2020, 44(3): 707-14.
[44] YI X, GAO H, CHEN D, et al. Effects of obesity and exercise on testicular leptin signal transduction and testosterone biosynthesis in male mice [J]. Am J Physiol Regul Integr Comp Physiol, 2017, 312(4): R501-R10.
[45] CHOI E, KIKUCHI S, GAO H, et al. Mitotic regulators and the SHP2-MAPK pathway promote IR endocytosis and feedback regulation of insulin signaling [J]. Nat Commun, 2019, 10: 1473.
[46] HUANG Q, XU H, WANG X, et al. Relationship between growth hormone deficiency and nonalcoholic fatty liver disease in patients with pituitary stalk interruption syndrome [J]. Clin Endocrinol, 2022, 97(5): 612-21.
[47] GAN Y, BUCKELS A, LIU Y, et al. Human GH receptor-IGF-1 receptor interaction: implications for GH signaling [J]. Mol Endocrinol, 2014, 28(11): 1841-54.
[48] DIELI-CONWRIGHT C M, COURNEYA K S, DEMARK-WAHNEFRIED W, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial [J]. J Clin Oncol, 2018, 36(9): 875-83.
[49] LI F H, SUN L, ZHU M, et al. Beneficial alterations in body composition, physical performance, oxidative stress, inflammatory markers, and adipocytokines induced by long-term high-intensity interval training in an aged rat model [J]. Exp Gerontol, 2018, 113: 150-62.
[50] VARCO-MERTH B, ROTWEIN P. Differential effects of STAT proteins on growth hormone-mediated IGF-I gene expression [J]. Am J Physiol Endocrinol Metab, 2014, 307(9): E847-E55.
[51] BARCLAY J L, NELSON C N, ISHIKAWA M, et al. GH-dependent STAT5 signaling plays an important role in hepatic lipid metabolism [J]. Endocrinology, 2011, 152(1): 181-92.
[52] FUKUDA I, HIZUKA N, YASUMOTO K, et al. Metabolic comorbidities revealed in patients with childhood-onset adult GH deficiency after cessation of GH replacement therapy for short stature [J]. Endocr J, 2008, 55(6): 977-84.
[53] TAKAHASHI Y, IIDA K, TAKAHASHI K, et al. Growth hormone reverses nonalcoholic steatohepatitis in a patient with adult growth hormone deficiency [J]. Gastroenterology, 2007, 132(3): 938-43.
[54] LIU Z, CORDOBA-CHACON J, KINEMAN R D, et al. Growth hormone control of hepatic lipid metabolism [J]. Diabetes, 2016, 65(12): 3598-609.
[55] MUELLER K M, KORNFELD J W, FRIEDBICHLER K, et al. Impairment of hepatic growth hormone and glucocorticoid receptor signaling causes steatosis and hepatocellular carcinoma in mice [J]. Hepatology, 2011, 54(4): 1398-409.
[56] VESTERLUND M, ZADJALI F, PERSSON T, et al. The SOCS2 ubiquitin ligase complex regulates growth hormone receptor levels [J]. PLoS One, 2011, 6(9): e25358.
[57] HATFIELD D L, KRAEMER W J, VOLEK J S, et al. Hormonal stress responses of growth hormone and insulin-like growth factor-I in highly resistance trained women and men [J]. Growth Horm IGF Res, 2021, 59: 101407.
[58] DROR N, PANTANOWITZ M, NEMET D, et al. High-intensity interval exercise test stimulates growth hormone secretion in children [J]. Growth Horm IGF Res, 2021, 57/58: 101388.
[59] SUGIHARTO, MERAWATI D, PRANOTO A, et al. Physiologi-

cal response of endurance exercise as a growth hormone mediator in adolescent women's [J]. J Basic Clin Physiol Pharmacol, 2022, 34(1): 61-7.

[60] STOKES K A, GILBERT K L, HALL G M, et al. Different responses of selected hormones to three types of exercise in young men [J]. Eur J Appl Physiol, 2013, 113(3): 775-83.

[61] HAGNER-DERENGOWSKA M, KALUZNY K, HAGNER W, et al. The effect of a 10-week nordic walking training program on the level of GH and LH in elderly women [J]. Climacteric, 2015, 18(6): 835-40.

[62] KONG X, HORIGUCHI N, MORI M, et al. Cytokines and STATs in liver fibrosis [J]. Front Physiol, 2012, 3: 69.

[63] HWANG S, FENG D, GAO B. Interleukin-22 acts as a mitochondrial protector [J]. Theranostics, 2020, 10(17): 7836-40.

[64] SAALIM M, RESHAM S, MANZOOR S, et al. IL-22: a promising candidate to inhibit viral-induced liver disease progression and hepatocellular carcinoma [J]. Tumor Biol, 2016, 37(1): 105-14.

[65] CHEN Z, DOWNING S, TZANAKAKIS E S. Four decades after the discovery of regenerating Islet-Derived (Reg) proteins: current understanding and challenges [J]. Front Cell Dev Biol, 2019, 7: 235.

[66] ZAI W, CHEN W, WU Z, et al. Targeted interleukin-22 gene delivery in the liver by polymetformin and penetratin-based hybrid nanoparticles to treat nonalcoholic fatty liver disease [J]. ACS Appl Mater Interfaces, 2019, 11(5): 4842-57.

[67] ABDELNABI M N, MOLINA M F, SOUCY G, et al. Sex-dependent hepatoprotective role of IL-22 receptor signaling in non-alcoholic fatty liver disease-related fibrosis [J]. Cell Mol Gastroenterol Hepatol, 2022, 14(6): 1269-94.

[68] OH J H, SCHUELER K L, STAPLETON D S, et al. Secretion of recombinant interleukin-22 by engineered lactobacillus reuteri reduces fatty liver disease in a mouse model of diet-induced obesity [J]. Msphere, 2020, 5(3): e00183-20.

[69] KONG X, FENG D, WANG H, et al. Interleukin-22 induces hepatic stellate cell senescence and restricts liver fibrosis in mice [J]. Hepatology, 2012, 56(3): 1150-9.

[70] RAMOS J S, DALLECK L C, STENNETT R C, et al. Effect of different volumes of interval training and continuous exercise on interleukin-22 in adults with metabolic syndrome: a randomized trial [J]. D Diabetes Metab Syndr Obes, 2020, 13: 2443-53.

[71] LI Y C, ZHENG X L, LIU B T, et al. Regulation of ATGL expression mediated by leptin *in vitro* in porcine adipocyte lipolysis [J]. Mol Cell Biochem, 2010, 333(1/2): 121-8.

[72] 宋刚, 张国栋, 雷小灿, 等. 耐力训练时脂肪甘油三酯脂肪酶与工作肌糖代谢和线粒体密度——基于ATGL基因敲除小鼠的研究[J]. 武汉体育学院学报(SONG G, ZHANG G D, LEI X C, et al. Adipose triglyceride lipase and working muscle glucose metabolism and mitochondrial density during endurance training: a study based on ATGL knockout mice [J]. J Wuhan Sports Univ), 2017, 51(10): 68-75.

[73] WU B, XU C, TIAN Y, et al. Aerobic exercise promotes the expression of ATGL and attenuates inflammation to improve hepatic steatosis via lncRNA SRA [J]. Sci Rep, 2022, 12(1): 5370.

[74] THUPARI J N, KIM E K, MORAN T H, et al. Chronic C75 treatment of diet-induced obese mice increases fat oxidation and reduces food intake to reduce adipose mass [J]. Am J Physiol Endocrinol Metab, 2004, 287(1): E97-E104.

[75] WILSON C G, TRAN J L, ERION D M, et al. Hepatocyte-specific disruption of CD36 attenuates fatty liver and improves insulin sensitivity in HFD-Fed mice [J]. Endocrinology, 2016, 157(2): 570-85.

[76] CHEN Y, LU W, JIN Z, et al. Carbenoxolone ameliorates hepatic lipid metabolism and inflammation in obese mice induced by high fat diet via regulating the JAK2/STAT3 signaling pathway [J]. Int Immunopharmacol, 2019, 74: 105498.

[77] LIU W, JING Z T, WU S X, et al. A novel AKT activator, SC79, prevents acute hepatic failure induced by Fas-mediated apoptosis of hepatocytes [J]. Am J Pathol, 2018, 188(5): 1171-82.

[78] 路瑛丽, 冯连世, 谢敏豪, 等. 高住高练对肥胖大鼠FAS mRNA和ATGL mRNA表达的影响[J]. 中国运动医学杂志(LU Y L, FENG L S, XIE M H, et al. Effect of high residence and high training on the expression of FAS mRNA and ATGL mRNA in obese rats [J]. Chin J Sports Med), 2014, 33(8): 785-9.

[79] SINGHAL G, KUMAR G, CHAN S, et al. Deficiency of fibroblast growth factor 21 (FGF21) promotes hepatocellular carcinoma (HCC) in mice on a long term obesogenic diet [J]. Mol Metab, 2018, 13: 56-66.

[80] YU J, ZHAO L, WANG A, et al. Growth hormone stimulates transcription of the fibroblast growth factor 21 gene in the liver through the signal transducer and activator of transcription 5 [J]. Endocrinology, 2012, 153(2): 750-8.

[81] SARGEANT J A, AITHAL G P, TAKAMURA T, et al. The influence of adiposity and acute exercise on circulating hepatokines in normal-weight and overweight/obese men [J]. Appl Physiol Nutr Metab, 2018, 43(5): 482-90.

[82] TANG H, TAN X, ZHU L, et al. Swimming prevents nonalcoholic fatty liver disease by reducing migration inhibitory factor through Akt suppression and autophagy activation [J]. Am J Transl Res, 2019, 11(7): 4315-25.

[83] LAI P F, BASKARAN R, KUO C H, et al. Bioactive dipeptide from potato protein hydrolysate combined with swimming exercise prevents high fat diet induced hepatocyte apoptosis by activating PI3K/Akt in SAMP8 mouse [J]. Mol Biol Rep, 2021, 48(3): 2629-37.

[84] 王佳倩, 李亚龙, 蒋昌君, 等. 有氧运动对AKT/GSK3β介导非酒精性脂肪肝肝细胞凋亡的影响[J]. 卫生研究(WANG J Q, LI Y L, JIANG C J, et al. Effect of aerobic exercise on AKT/GSK3β-mediated apoptosis in nonalcoholic fatty liver cells [J]. J Hyg Res), 2023, 52(2): 246-52.

[85] CHOWDHRY S, NAZMY M H, MEAKIN P J, et al. Loss of Nrf2 markedly exacerbates nonalcoholic steatohepatitis [J]. Free Radic Biol Med, 2010, 48(2): 357-71.

[86] BATAILLE A M, MANAUTOU J E. Nrf2: a potential target for new therapeutics in liver disease [J]. Clin Pharmacol Ther, 2012, 92(3): 340-8.

[87] ZOU Y, CHEN Z, SUN C, et al. Exercise intervention mitigates pathological liver changes in NAFLD zebrafish by activating SIRT1/AMPK/NRF2 signaling [J]. Int J Mol Sci, 2021, 22(20): 10940.

[88] YU H, JIANG X, DONG F, et al. Lipid accumulation-induced hepatocyte senescence regulates the activation of hepatic stellate cells through the Nrf2-antioxidant response element pathway [J]. Exp Cell Res, 2021, 405(2): 112689.

[89] BANERJEE S, BIEHL A, GADINA M, et al. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects [J]. Drugs, 2017, 77(5): 521-46.

[90] KHALAFI M, SYMONDS M E. The impact of high-intensity interval training on inflammatory markers in metabolic disorders: a meta-analysis [J]. Scand J Med Sci Sports, 2020, 30(11): 2020-36.

[91] YEH W J, KO J, CHENG W Y, et al. Diet containing dehulled adlay ameliorates hepatic steatosis, inflammation and insulin resistance in rats with non-alcoholic fatty liver disease [J]. Br J Nutr, 2021, 128(3): 369-76.

[92] SPANGENBURG E E, BROWN D A, JOHNSON M S, et al. Exercise increases SOCS-3 expression in rat skeletal muscle: potential relationship to IL-6 expression [J]. J Physiol-Lond, 2006, 572(3): 839-48.

[93] KYU-MIN P, KIMZEONE, LEE U. The influence of participation in an after-school exercise program on growth-related factors, insulin resistance, and blood lipids in overweight and obese high school girlsitle of manuscript in English [J]. Korean Soc Sport Sci, 2018, 27(3): 1239-49.

[94] ZHANG H, TONG T K, KONG Z, et al. Exercise training-induced visceral fat loss in obese women: the role of training intensity and modality [J]. Scand J Med Sci Sports, 2021, 31(1): 30-43.

[95] LEE J, PARK H, AHN J Y, et al. The effects of moderate-intensity aerobic exercise following fasting on blood FGF21, IL-6 levels, and energy metabolism in obese men [J]. Korean J Sport Stud, 2018, 57(4): 333-44.

[96] DINIZ T A, DE LIMA JUNIOR E A, TEIXEIRA A A, et al. Aerobic training improves NAFLD markers and insulin resistance through AMPK-PPAR-alpha signaling in obese mice [J]. Life Sci, 2021, 266: 118868.

[97] 郭项英, 彭子富, 何亦敏, 等. MiRNA-122在运动改善非酒精性脂肪肝中的作用[J]. 中国组织工程研究(GUO X Y, PENG Z F, HE Y M, et al. Role of MiRNA-122 in the improvement of nonalcoholic fatty liver by exercise [J]. Chin J Tissue Eng Res), 27(10): 1-10.