

高强度间歇训练和司美格鲁肽通过IL-17/CXCL1 通路改善代谢功能障碍相关脂肪性肝病

王紫玉^{1,2} 康正鸿¹ 邢思思¹ 柳华^{3*}

(¹武汉体育学院研究生院, 武汉 430079; ²武汉亚洲心脏病医院, 武汉 430022;

³武汉体育学院体质监测与慢性病研究中心, 武汉 430079)

摘要 该研究旨在探究8周高强度间歇训练(high-intensity interval training, HIIT)和司美格鲁肽(semaglutide)对2型糖尿病合并代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)小鼠肝脏炎症的分子机制。研究选取10只8周龄健康db/db小鼠作为对照组(DC), 30只同周龄db/db小鼠被随机分为运动组(DE)、药物组(DM)、联合干预组(EM), 每组10只。DE组、EM组进行持续8周的HIIT运动干预, DM组和EM组进行8周semaglutide颈部皮下注射处理(0.05 mg/kg), 实验期间每周定时监测小鼠体质量及空腹血糖。干预结束后, 各组选取3例肝脏组织进行转录组测序, 筛选差异表达基因(DEGs), 并进行基因集富集分析(Gene Set Enrichment Analysis, GSEA)、蛋白-蛋白互作(PPI)网络分析。油红O及苏木精-伊红(hematoxylin-eosin, HE)染色法观察小鼠肝脏病理性改变状况; Masson染色观察肝脏纤维化; 试剂盒测定肝功能和血脂四项; qRT-PCR测定*Cxcl1* mRNA表达水平; Western blot法检测肝脏中炎症因子、IL-17信号通路、纤维化相关蛋白表达情况。结果表明, 与DC组相比, DE、DM、EM组小鼠体质量、空腹血糖、摄食量、肝脏质量及血清TG、TC、AST、ALT、HDL-C、LDL-C含量均下降; HE、油红O染色、Masson染色结果显示, DC组肝细胞气球样变及脂质沉积严重, 炎细胞浸润并在汇管区出现些许蓝色胶原沉积, 而DE组、DM组、EM组肝细胞气球样变、炎细胞浸润和胶原沉积情况均得到改善。转录组学结果提示, IL-17信号通路蛋白及差异基因*Cxcl1*表达在DE、DM、EM组中显著下调; qRT-PCR结果显示, DE、DM、EM组相较于DC组, *Cxcl1*的mRNA表达水平均下降。Western blot结果显示, 与DC组相比, DE组肝脏中TNF- α 、IL-6、Pro-IL-1 β 、Cleaved-IL-1 β 、IL-17A、p-NF- κ B/NF- κ B值及趋化因子CXCL1蛋白表达水平显著降低。DM组和EM组亦可不同程度下调p-NF- κ B/NF- κ B值及多种炎症因子(TNF- α 、IL-6、IL-1 β 、IL-17A)和CXCL1的表达。与DE组相比, DM组p-NF- κ B/NF- κ B值及IL-6、IL-1 β 、IL-17A和CXCL1表达水平明显升高, 而EM组p-NF- κ B/NF- κ B值、CXCL1表达水平升高, 其余炎症指标无显著差异。进一步检测TGF- β /Smad通路相关蛋白发现, 与DC组相比, DE、DM及EM组TGF- β 1、 α -SMA及p-Smad2/3蛋白表达显著下调, Smad2/3总蛋白水平在各组间无明显差异。与DE组相比, TGF- β 1在DM组、 α -SMA在DM组和EM组中蛋白表达有所上调。综上, 8周HIIT与司美格鲁肽干预均可有效延缓db/db小鼠MASLD的病理进展, 显著改善肝功能, 抑制肝脏炎症反应并减轻肝纤维化损伤, 其作用机制可能与抑制IL-17/NF- κ B/CXCL1信号通路的过度激活相关。

关键词 代谢功能障碍相关脂肪性肝病; 高强度间歇训练; 司美格鲁肽; 炎症; db/db小鼠

收稿日期: 2026-05-18

接受日期: 2026-08-31

国家自然科学基金(批准号: 32471503)和湖北省教育厅科学研究计划资助项目重点项目(批准号: D20224102)资助的课题

*通信作者。Tel: 13407158577, E-mail: hualihua2005@163.com

Received: May 18, 2026

Accepted: August 31, 2026

This work was supported by the National Natural Science Foundation of China (Grant No.32471503) and the Key Project of Scientific Research Plan of Hubei Provincial Department of Education (Grant No.D20224102)

*Corresponding author. Tel: +86-13407158577, E-mail: hualihua2005@163.com

High-Intensity Interval Training and Semaglutide Ameliorate Metabolic Dysfunction-Associated Steatotic Liver Disease via the IL-17/CXCL1 Pathway

WANG Ziyu^{1,2}, KANG Zhenghong¹, XING Sisi¹, LIU Hua^{3*}

(¹Graduate School, Wuhan Sports University, Wuhan 430079, China; ²Wuhan Asia Heart Hospital, Wuhan 430022, China;

³Laboratory of Physical Fitness Monitoring & Chronic Disease Intervention, Wuhan Sports University, Wuhan 430079, China)

Abstract This study was to explore the molecular mechanisms underlying the effects of 8-week high-intensity interval training and semaglutide on hepatic inflammation in db/db mice with type 2 diabetes mellitus complicated with metabolic dysfunction-associated steatotic liver disease. A total of 10 healthy 8-week-old db/db mice were assigned to the control group, and another 30 age-matched db/db mice were randomly divided into DE group, DM group and EM group, with 10 mice in each group. Mice in DE and EM groups received 8-week HIIT intervention; mice in DM and EM groups were subjected to subcutaneous neck injection of semaglutide at a dose of 0.05 mg/kg for 8 consecutive weeks. Body mass and fasting blood glucose of mice were regularly monitored every week throughout the experiment. After intervention, three liver tissue samples were selected from each group for transcriptome sequencing to screen differentially expressed genes, followed by Gene Set Enrichment Analysis and protein-protein interaction network analysis. Oil red O and hematoxylin-eosin staining were used to observe hepatic pathological changes, and Masson staining was applied to evaluate liver fibrosis. Liver function indexes were detected using commercial assay kits. The mRNA expression levels of inflammation-related genes were determined by quantitative real-time polymerase chain reaction. Western blot was performed to detect the protein levels of inflammatory factors, IL-17 signaling pathway molecules and fibrosis-related proteins in liver tissues. The results show that compared with the DC group, the body mass, fasting blood glucose, food intake, liver mass, as well as serum levels of TG, TC, AST, ALT, HDL-C and LDL-C were significantly decreased in DE, DM and EM groups. HE, oil red O and Masson staining results revealed severe hepatocellular ballooning degeneration, massive lipid deposition, inflammatory cell infiltration and partial collagen deposition in the portal area of DC group. In contrast, hepatocellular ballooning degeneration, inflammatory infiltration and collagen deposition were markedly ameliorated in DE, DM and EM groups. Transcriptomic analysis indicated that the IL-17 signaling pathway and the differential gene *Cxcl1* were significantly downregulated in DE, DM and EM groups. qRT-PCR results further verified that the mRNA expression of *Cxcl1* was notably reduced in the three intervention groups relative to the DC group. Western blot results showed that the protein expressions of TNF- α , IL-6, Pro-IL-1 β , Cleaved-IL-1 β , IL-17A, the ratio of p-NF- κ B/NF- κ B and chemokine CXCL1 were dramatically lowered in the DE group vs the DC group. The DM and EM groups also downregulate the p-NF- κ B/NF- κ B ratio as well as the expressions of multiple inflammatory factors (TNF- α , IL-6, IL-1 β , IL-17A) and CXCL1 to varying degrees. Compared with the DE group, the p-NF- κ B/NF- κ B ratio and the expressions of IL-6, IL-1 β , IL-17A and CXCL1 were obviously elevated in the DM group. Only the p-NF- κ B/NF- κ B ratio and CXCL1 expression were increased in the EM group, with no significant differences in other inflammatory indicators. Further detection of TGF- β /Smad signaling pathway-related proteins demonstrated that the protein levels of TGF- β 1, α -SMA and p-Smad2/3 were prominently downregulated in DE, DM and EM groups compared with the DC group, while the total protein expression of Smad2/3 showed no significant difference among all groups. Compared with the DE group, TGF- β 1 expression was upregulated in the DM group, and α -SMA expression was increased in both DM and EM groups. In conclusion, 8-week HIIT and semaglutide interventions can effectively retard the pathological progression of MASLD in db/db mice by ameliorating liver dysfunction, suppressing hepatic inflammation, and attenuating hepatic fibrosis. The underlying mechanism may be

attributed to the inhibition of the excessive activation of the IL-17/NF- κ B/CXCL1 signaling axis.

Keywords MASLD; HIIT; semaglutide; inflammation; db/db mice

糖尿病(diabetes mellitus, DM)患病人数在全球范围内呈上升趋势,预计到2050年将影响约8.53亿人^[1]。2型糖尿病(type 2 diabetes mellitus, T2DM)是一种慢性代谢性疾病,其特征是胰岛素抵抗和胰岛 β 细胞功能减退从而导致持续高血糖和代谢紊乱。与非T2DM患者相比,T2DM患者发生视网膜病变、终末期肾病、肝病和心血管疾病等并发症的风险明显更高^[2]。长期的T2DM患者往往合并肥胖、血脂异常等代谢综合征,增加肝脏脂肪沉积的风险^[3]。全球范围内,肝脏脂肪沉积在T2DM患者中的患病率约为66.7%,合并代谢异常会进一步增加该患病风险^[4]。

代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD),原称为非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD),是一种以肝细胞发生大泡性或微泡性脂肪变性为主要病理特征,并至少合并一项代谢异常的脂肪肝病^[5]。MASLD的并发症包括代谢功能障碍相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)、肝硬化和肝细胞癌(hepatocellular carcinoma, HCC),是导致肝脏相关疾病和死亡的主要原因^[6]。研究表明,MASLD会使患2型糖尿病的风险增加2至5倍^[7],因此被认为是T2DM的主要病因之一,而T2DM也会反向促进脂肪肝相关并发症MASLD的发生^[8]。基于MASLD的发生发展与2型糖尿病、肥胖及胰岛素抵抗高度共存,针对代谢异常的综合干预已成为当前防治MASLD的重要策略^[9]。

司美格鲁肽(semaglutide)是一种胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)受体激动剂,已被FDA批准用于治疗糖尿病和肥胖症^[10-11]。在2型糖尿病治疗中,司美格鲁肽除改善血糖代谢外,还可在一定程度上发挥心血管保护作用^[12],改善糖尿病相关认知功能障碍,并降低慢性肾病进展风险^[13]。研究表明,司美格鲁肽还涉及炎症及免疫相关通路的调节,通过下调巨噬细胞中的IRE1 α -XBP1-C/EBP α 信号通路,显著降低肝组织中炎症标志物(TNF- α 、IL-6、MCP-1)的表达水平,减少巨噬细胞浸润从而减轻肝脏炎症反应^[14]。无论是短期运动还是长期运动都能减少肝脏脂肪堆积,减轻炎症反应从而延缓肝纤维化的进展^[15]。高强度间歇训练(high-intensity

interval training, HIIT)对MASLD的保护作用可归因于不同的机制,包括降低肝脏脂肪含量、抑制肝纤维化、减轻炎症浸润、减少肝细胞凋亡以及缓解氧化应激^[16-17]。研究表明,运动可以通过减少促炎细胞因子分泌、抑制巨噬细胞浸润来减轻MASH特征性肝脏炎症损伤^[18-19]。近年来,IL-17信号通路因其在MASLD炎症进展中的核心作用而备受关注。肥胖和MASLD常伴随系统性Th17免疫偏移,其中IL-17A被认为是驱动肝脏炎症反应的关键因子^[22]。已有研究表明,MASLD进程中IL-17相关信号持续激活,导致多种趋化因子和促炎细胞因子表达水平升高,从而促进髓系细胞及T细胞向肝脏募集,加速炎症反应和肝病进展^[23]。在这些因子中,趋化因子CXCL1在肝纤维化的发生与发展中发挥重要作用,其过度表达不仅可驱动中性粒细胞浸润,还可通过促进肝星状细胞活化而加速纤维化进程^[24]。然而有研究指出,降糖药物可能会干扰运动引起的降糖作用,且运动和药物干预在不同MASLD病理阶段中的疗效亦存在差异^[20-21]。运动与药物可能并非简单的协同叠加关系,而是在代谢调控、炎症反应及组织重塑等层面存在作用机制上的差异甚至潜在拮抗。基于此,本研究通过对db/db小鼠进行HIIT、司美格鲁肽以及二者联合干预,探讨IL-17/CXCL1通路在MASLD炎症进展中的作用,并进一步关注其与TGF- β 通路的关联,为运动与药物干预肝脏炎症提供实验依据。

1 材料与方法

1.1 动物分组

40只8周健康雄性SPF级db/db(C57BLKS/J)小鼠,购于杭州子源实验动物科技有限公司。小鼠适应性喂养1周后,采用随机数字法将其分为糖尿病对照组(DC组,10只)、运动组(DE组,10只)、药物组(DM组,10只)和联合干预组(EM组,10只)。所有动物均处于12:12的暗/光循环中,湿度为40%,温度为22℃。每周监测体质量和血糖水平,同时每天记录食物摄入量。本研究动物实验方案得到了武汉体育学院动物伦理委员会批准(批准号:S0087-20230714-01)。

1.2 材料与主要试剂

TNF- α (货号:ab6671)购自英国Abcam公司;

IL-6、 α -SMA、IL-17A、p-NF- κ B、Smad2/3、p-Smad2/3(货号: 12912S、14968S、13838S、3033S、3102S、9510S)购自美国Cell Signaling Technology公司; IL-1 β (货号: AF4006)购自Affinity Biosciences公司; CXCL1、NF- κ B、 β -actin、GAPDH(货号: 12335-1-AP、10745-1-AP、60008-1-Ig、60004-1-Ig)购自武汉三鹰生物技术有限公司; TGF- β 1(货号: GB11179)购自武汉赛维尔生物科技有限公司; 实时荧光定量PCR试剂盒(货号: 208052)购自德国QIAGEN公司; 甘油三酯(triglyceride, TG)、总胆固醇(total cholesterol, TC)、天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)、丙氨酸氨基转移酶(alanine aminotransferase, ALT)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)检测试剂盒(货号: A110-1-1、A111-1-1、C010-2-1、C009-2-1、A112-1-1、A113-1-1)均购自南京建成生物工程研究所。

1.3 干预方法

1.3.1 HIIT干预 小鼠在跑台上进行高强度间歇训练, 每次训练包括10组循环, 每组以(85%~90%) $V_{\max}$ 运动4 min, 随后以(30%~40%) $V_{\max}$ 运动2 min。训练频率为每周5 d, 持续8周^[25]。

1.3.2 司美格鲁肽干预 DM组与EM组db/db小鼠每日按5 mL/kg的剂量, 皮下注射semaglutide[诺和诺德(中国)制药有限公司] 0.05 mg/kg, 连续给药8周, 作为对照, DC组与DE组小鼠则每日接受等体积的生理盐水注射^[26]。

1.4 组织取材及处理

每周定期测量db/db小鼠体质量, 并检测小鼠空腹血糖(fasting blood glucose, FBG)。在末次跑台运动结束后, 各组小鼠均禁食12 h, 不禁水。实验结束后用异氟烷气麻醉, 通过眼眶取血收集小鼠全血, 采集肝脏称取湿重后装入冻存管, 于-80 °C冰箱中长期保存用于后续实验; 并取小鼠部分肝脏右叶置于4%多聚甲醛溶液中, 于常温固定24 h, 用于后续石蜡包埋并行HE染色; 另取肝组织制备冰冻切片, 行油红O染色。

1.5 HE染色

组织标本经石蜡包埋、切片后行苏木精-伊红染色, 光学显微镜下每张切片随机选取3个不重叠视

野采集图像, 收集相同放大倍数的图像进行观察, 评估肝脏病理学变化。

1.6 油红O染色

肝组织脱水后制备10 μ m冰冻切片, 行油红O染色, 显微镜下拍照并分析肝组织脂质沉积情况。

1.7 Masson染色

小鼠的肝脏组织石蜡切片脱蜡水化后行Masson三色染色, 切片经过无水乙醇脱水、透明封片后, 用显微镜观察染色情况并收集图像。

1.8 试剂盒测定

实验结束后小鼠眼球取血, 血样室温静置2 h后, 4 °C、3 000 r/min离心15 min, 重复2次, 取得上层血清。血清中TG、TC、ALT、AST、HDL-C及LDL-C水平通过检测试剂盒(南京建成生物工程研究所)测量。所有步骤均根据制造商推荐的方案进行。

1.9 蛋白免疫印迹

冻存的样品与RIPA裂解缓冲液混合, 涡旋(60 Hz、60 s), 离心(12 000 $\times$ g、4 °C、15 min)收集上清液, 采用BCA法测定蛋白浓度。随后进行上样、电泳、转膜、封闭, 分别用TNF- α (1:1 000)、IL-6(1:1 000)、IL-1 β (1:1 000)、 α -SMA(1:2 000)、IL-17A(1:1 000)、CXCL1(1:1 000)、NF- κ B(1:1 000)、p-NF- κ B(1:1 000)、Smad2/3(1:1 000)、p-Smad2/3(1:1 000)、 β -actin(1:10 000)、GAPDH(1:50 000)、TGF- β 1(1:1 000)抗体4 °C孵育过夜, TBST洗膜后二抗(1:5 000)室温孵育1 h。使用ECL发光液显影, 曝光后用ImageJ软件分析。

1.10 qRT-PCR检测相关蛋白mRNA水平

使用TRIzol法提取肝组织总RNA, 测定RNA浓度后按照反转录试剂盒说明书操作获得cDNA产物。用Step One Plus型荧光定量PCR仪通过SYBR Green染料法检测目的基因表达水平, 引物序列如下。Cxcl1-F: 5'-CGC CTA TCG CCA ATG AGCT-3', Cxcl1-R: 5'-GCA ACA CCT TCA AGC TCT GGA-3'。反应程序: 95 °C预变性3 min; 95 °C变性7 s, 58 °C退火35 s, 72 °C延伸35 s, 40个循环。每个样本均设置3个复孔。以GAPDH作为对照, 通过SYBR实时荧光定量试剂盒进行扩增反应, 结果采用 $2^{-\Delta\Delta C_t}$ 法进行计算。

1.11 转录组学测序

各组随机选取3只小鼠, 取肝脏组织进行RNA的提取及文库的建立。RNA-seq文库由CapitalBio

Technology生成和测序,使用Nanodrop检测RNA样本纯度,采用Agilent 2100 Bioanalyzer测定RNA的RIN值,评估RNA完整性和降解程度。再经过PCR扩增纯化等,最终得到构建完成的文库;然后进行测序及质控分析和序列比对分析;对上述过程得到的基因检测结果进行表达量与差异表达分析,当 $|\log_2FC|>1.5$ 且 P 值 <0.05 时被确定为差异表达基因。

1.12 统计分析

所有统计学分析均通过GraphPad Prism 9.5软件完成,定量数据以平均值 $\pm$ 标准差($\bar{x}\pm s$)表示。多组比较使用双因素方差分析(Two-Way ANOVA),并进行Tukey事后检验。单因素方差分析(One-Way ANOVA)用于比较各组的平均变化,并进行Dunnett多重比较检验。以 $P<0.05$ 为差异具有统计学意义。

2 结果

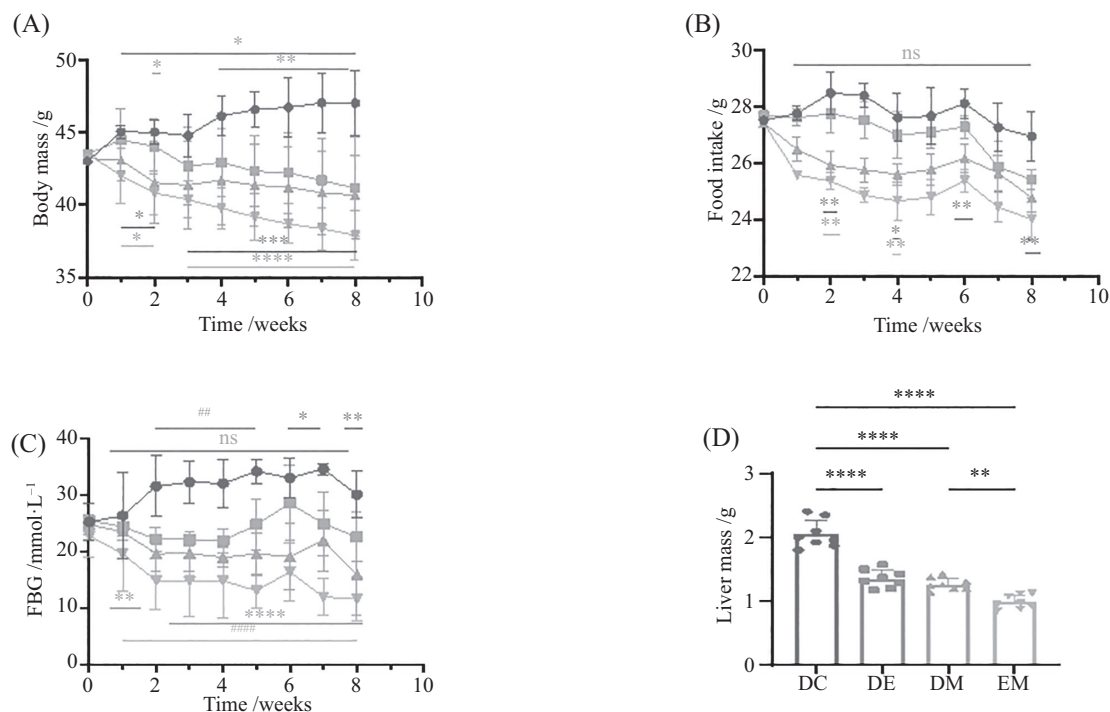
2.1 HIIT和司美格鲁肽对db/db小鼠体质量和空腹血糖的影响

db/db小鼠的体质量、摄食量、血糖如图1A~图1C所示,经8周药物、运动及联合干预后,不同干

预方式对小鼠体质量有显著影响。在2~5周,DC组体质量高于DE组($P<0.05$)、DM组($P<0.01$)和EM组($P<0.01$),6~8周体质量下降无显著性差异。HIIT及司美格鲁肽干预这两种干预方式均不同程度地显著抑制了T2DM引起的体质量增加,其中联合干预减重效果最佳。

摄食量结果显示,与DC组相比,DE组和EM组的食物摄入量在前5周显著减少,然而第6周各组摄入量略有回升。7~8周DE组和EM组摄食量显著降低,且EM组改善效果最佳。

每周小鼠空腹血糖结果显示,DC组小鼠显示出明显的高血糖症,并在第3周开始血糖值上升趋势逐渐平稳。从第5周开始,DE组、DM组、EM组的血糖变化出现拐点,降血糖效应开始显现,DM和EM组的FBG显著下降。8周干预结束后,DE组、DM组、EM组小鼠空腹血糖水平均低于DC组小鼠。小鼠死后对其肝脏进行称重(图1D),DC组db/db小鼠肝脏体质量高于DE、DM、EM组($P<0.001$),EM组小鼠肝脏质量改善效果最为显著。综上,运动组、药物组及联合干预组小鼠的体质量、空腹血糖、摄食量

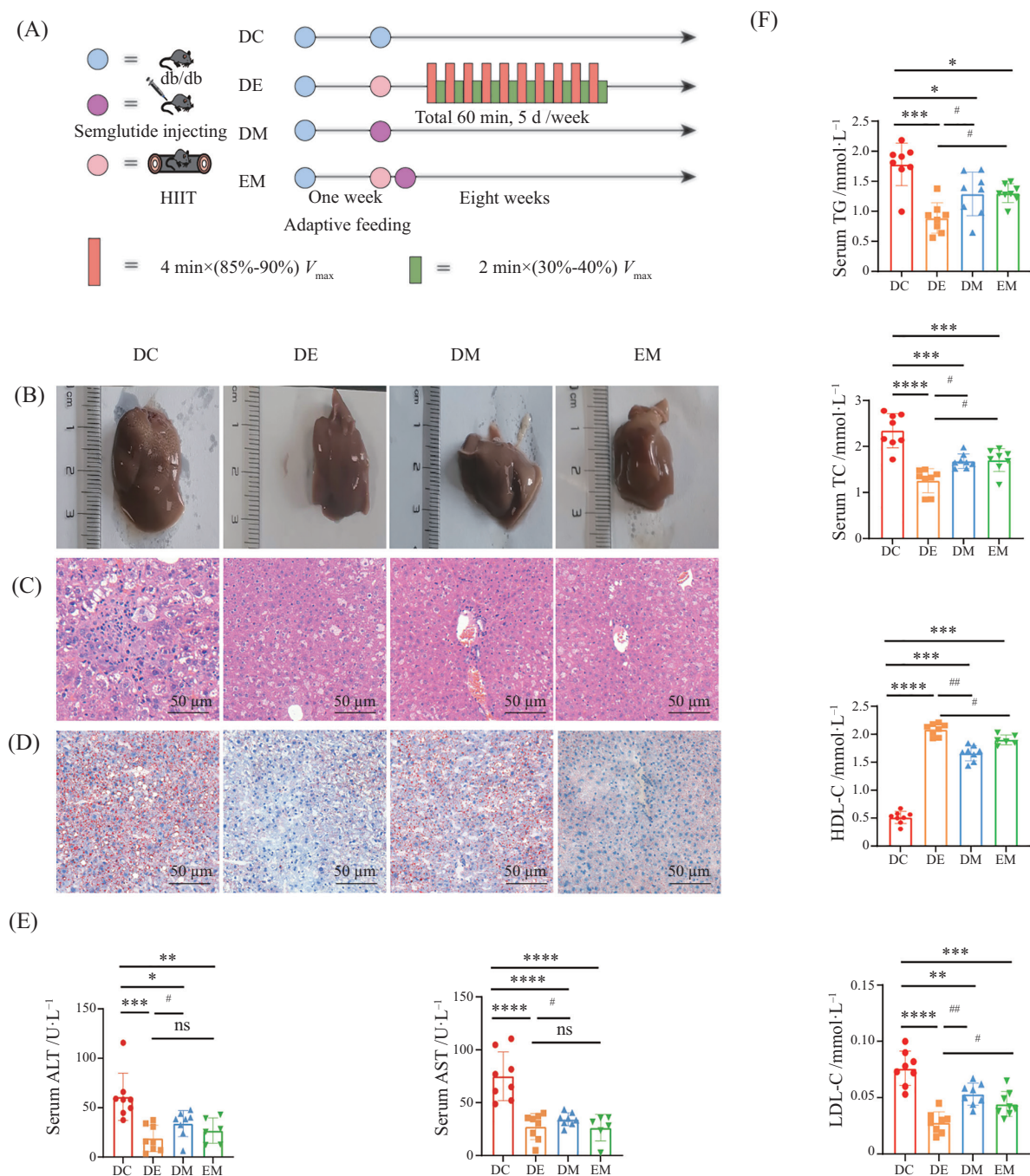


A: 体质量; B: 摄食量; C: 空腹血糖; D: 肝脏质量。n=6。ns: $P>0.05$, * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; ## $P<0.01$, #### $P<0.0001$ 。

A: body mass; B: food intake; C: FBG; D: liver mass. n=6. ns: $P>0.05$, * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; ## $P<0.01$, #### $P<0.0001$ 。

图1 HIIT和semaglutide及联合干预对db/db小鼠体质量、血糖、摄食量和肝脏质量的影响

Fig.1 Effects of HIIT, semaglutide and their combined intervention on body mass, blood glucose, food intake and liver mass in db/db mice



A: HIIT和semaglutide的干预方案; B: 各组肝脏外观; C: 各组HE染色($n=4$); D: 各组油红O染色($n=4$); E、F: 血清ALT、AST、TG、TC、HDL-C、LDL-C的含量。ns: $P>0.05$, * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; # $P<0.05$, ## $P<0.01$ 。 $n=8$ 。

A: intervention protocols for HIIT and semaglutide; B: gross liver morphology of each group; C: HE staining of each group ($n=4$); D: oil red O staining of each group ($n=4$); E,F: serum levels of ALT, AST, TG, TC, HDL-C and LDL-C. ns: $P>0.05$, * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; # $P<0.05$, ## $P<0.01$. $n=8$.

图2 HIIT和semaglutide及联合干预对db/db小鼠肝脏病理学和肝功能的影响

Fig.2 Effects of HIIT, semaglutide and their combined intervention on liver pathology and liver function in db/db mice

和肝脏质量均有显著改善。

2.2 8周HIIT和司美格鲁肽及其联合干预可改善肝脏脂质沉积

肝组织肉眼观察可见DC组肝脏体积增大,局部

奶黄色,包膜油腻且难剥离(图2B)。DE组、DM组及EM组肝脏色泽、弹性及质地较DC组改善。HE结果(图2C)显示,DC组细胞排列紊乱,肿胀呈椭圆,DE组和EM组细胞排列较规整,胞质内大泡样改变减轻,而

药物组仍可见细胞排列紊乱及核移位。图红O染色(图2D)显示, DC组脂滴广泛弥散分布。DE组及EM组脂滴数量减少, 体积减小且分布稀疏, DM组改善相对较轻。与DC组相比(图2E和图2F), DE组、DM组、EM组小鼠血清中TG、TC、LDL-C含量显著降低, HDL-C含量显著升高; 与DE组相比, DM和EM组TG、TC、LDL-C含量上升, HDL-C含量下降。肝功能结果显示, DC组血清中ALT和AST酶活性高于DM组、EM组、DE组; 与DE组相比, DM组改善结果稍差, 而EM组无显著性变化。这提示高强度间歇训练、药物干预及联合干预都缓解了db/db小鼠肝脏损伤情况, 其中运动改善最为明显。

2.3 肝脏转录组学研究

2.3.1 db/db小鼠肝脏mRNA表达量差异分析 小鼠肝脏 mRNA表达量差异分析图如图3所示。Venn图显示, DC vs DM与DC vs EM共同差异表达基因121个, DC vs DM与DC vs DE共同差异表达基因57个, DC vs EM与DC vs DE共同差异表达基因37个。三个比较组共鉴定出76个差异表达基因, 将这些差异表达基因基于STRING数据集, 我们预测了在运动组、药物组和联合干预组中上调或下调的失调基因编码的蛋白质, 来构建PPI网络(图3B), 并使用cytoscape进行了可视化。基于CytoNCA工具, 通过对度中心性进行排序来识别中心基因。排名前10位的基因为*Timd4*、*Siglec1*、*Adgre4*、*Itgal*、*Il1r1*、*Fcgr4*、*Marco*、*Cxcl1*、*Csflr*、*Tlr2*, 这些基因可能

对运动及药物干预至关重要。

2.3.2 db/db小鼠肝脏 mRNA 差异表达基因功能富集分析 利用 GSEA 富集分析进一步分析了 DE、DM、EM 组中差异基因的表达情况, 如图 4A~图 C 所示, DE 组、DM 组、EM 组前五条通路均与炎症、免疫、代谢等相关通路有关。其中 DE 组前五条提示与 IL-17 信号通路、嘧啶代谢、转录失调、TH17 细胞分化等通路有关, DM 组与 PI3K/AKT、系统性红斑狼疮、NF- κ B 信号通路、类固醇激素生物合成、IL-17 信号通路等通路有关。EM 组与碳代谢、IL-17 信号通路、氨基酸生物合成、NOD 样受体信号通路有关。

2.3.3 差异基因的PCR验证 基于转录组学分析结果, 进一步验证 *Cxcl1* 基因在各组小鼠中的表达水平。与DC组相比(图5E), DE组和DM组的 *Cxcl1* mRNA表达下调($P<0.0001$; $P<0.01$), EM组表达下调($P<0.001$)。

2.4 HIIT和司美格鲁肽及其联合干预对IL-17信号通路相关蛋白表达的影响

采用 Western blot法检测各组小鼠肝脏组织 IL-17A、NF- κ B、p-NF- κ B、TNF- α 、IL-6及 IL-1 β 蛋白的表达情况,图 5C和图 5D可看出,与 DC组相比,DE组炎症因子 TNF- α 、Pro-IL-1 β 、Cleaved-IL-1 β 、IL-6蛋白含量显著降低,IL-17A、p-NF- κ B/NF- κ B值和 CXCL1的表达水平显著降低。药物和联合干预均可降低 IL-6、IL-1 β 的表达水平,并下调 IL-17A、

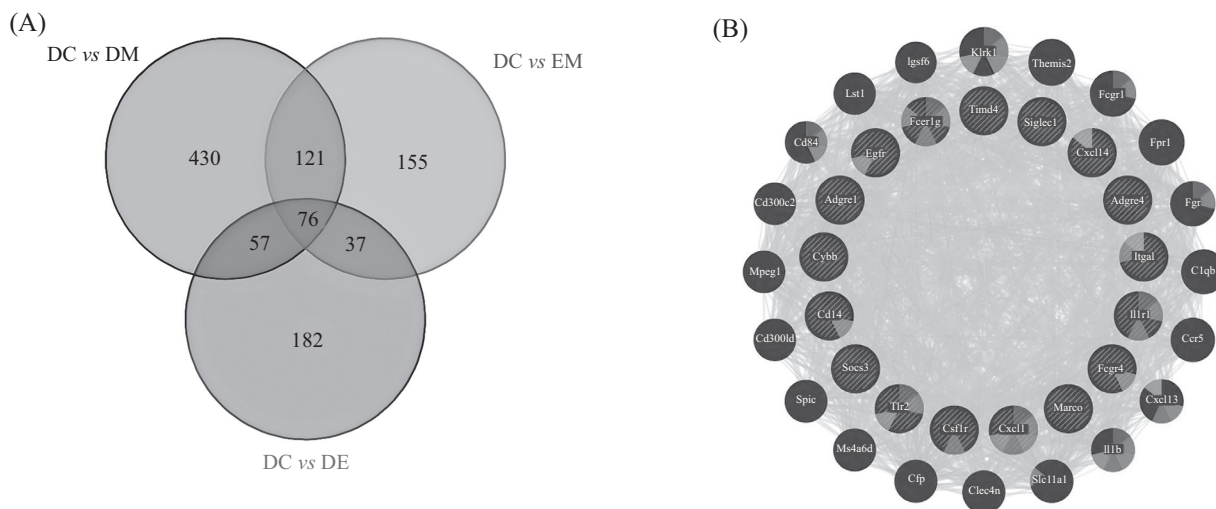
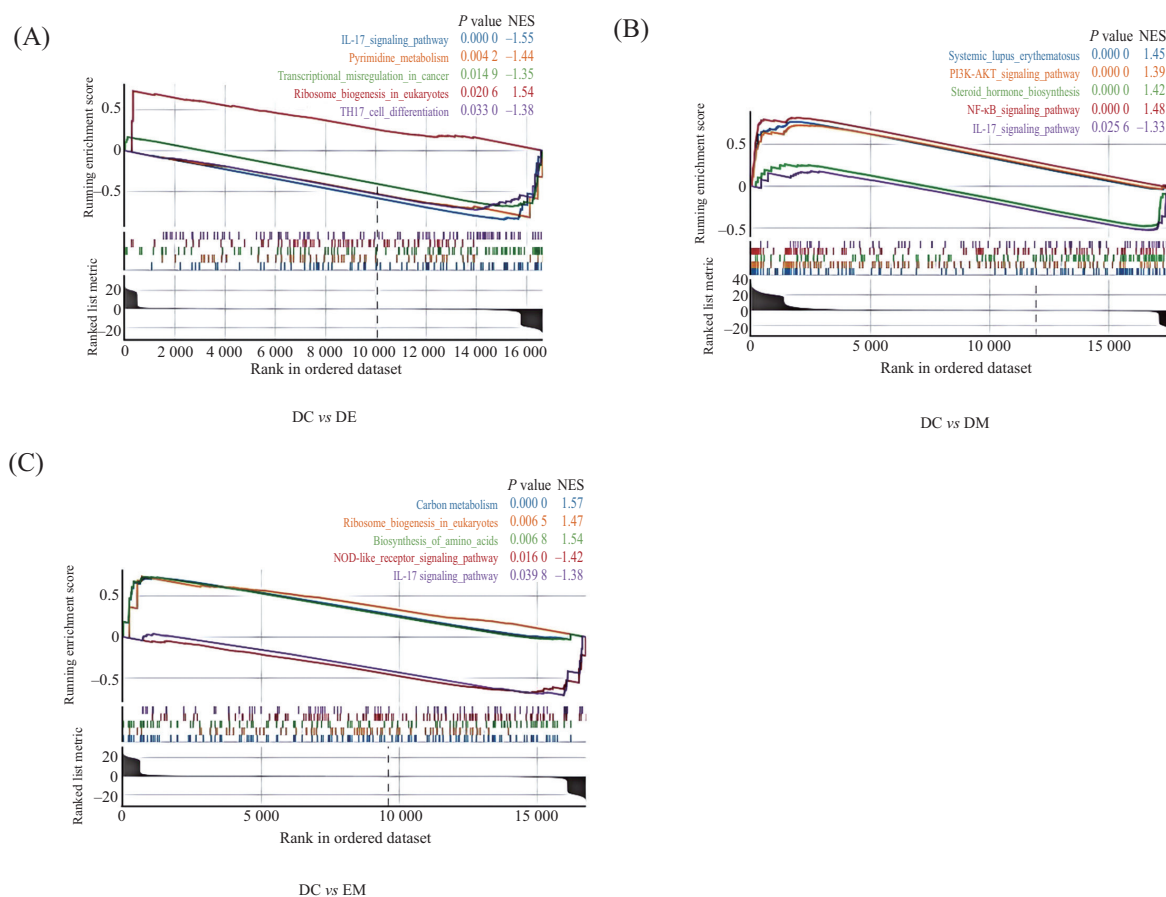


图3 不同干预方式对转录组的影响
Fig.3 Effects of different interventions on the transcriptome



A: 对照组vs运动组; B: 对照组vs药物组; C: 对照组vs联合干预组。

A: DC vs DE; B: DC vs DM; C: DC vs EM.

图4 GSEA通路富集分析

Fig.4 GSEA pathway enrichment analysis

CXCL1、p-NF- κ B/NF- κ B表达。与DE组相比, DM和EM组IL-17A、CXCL1、p-NF- κ B/NF- κ B表达水平升高, DE组炎症因子IL-6、IL-1 β 的表达水平升高。以上结果提示运动干预抑制IL-17信号通路更为显著。

2.5 HIIT和司美格鲁肽及其联合干预对纤维化通路相关蛋白表达的影响

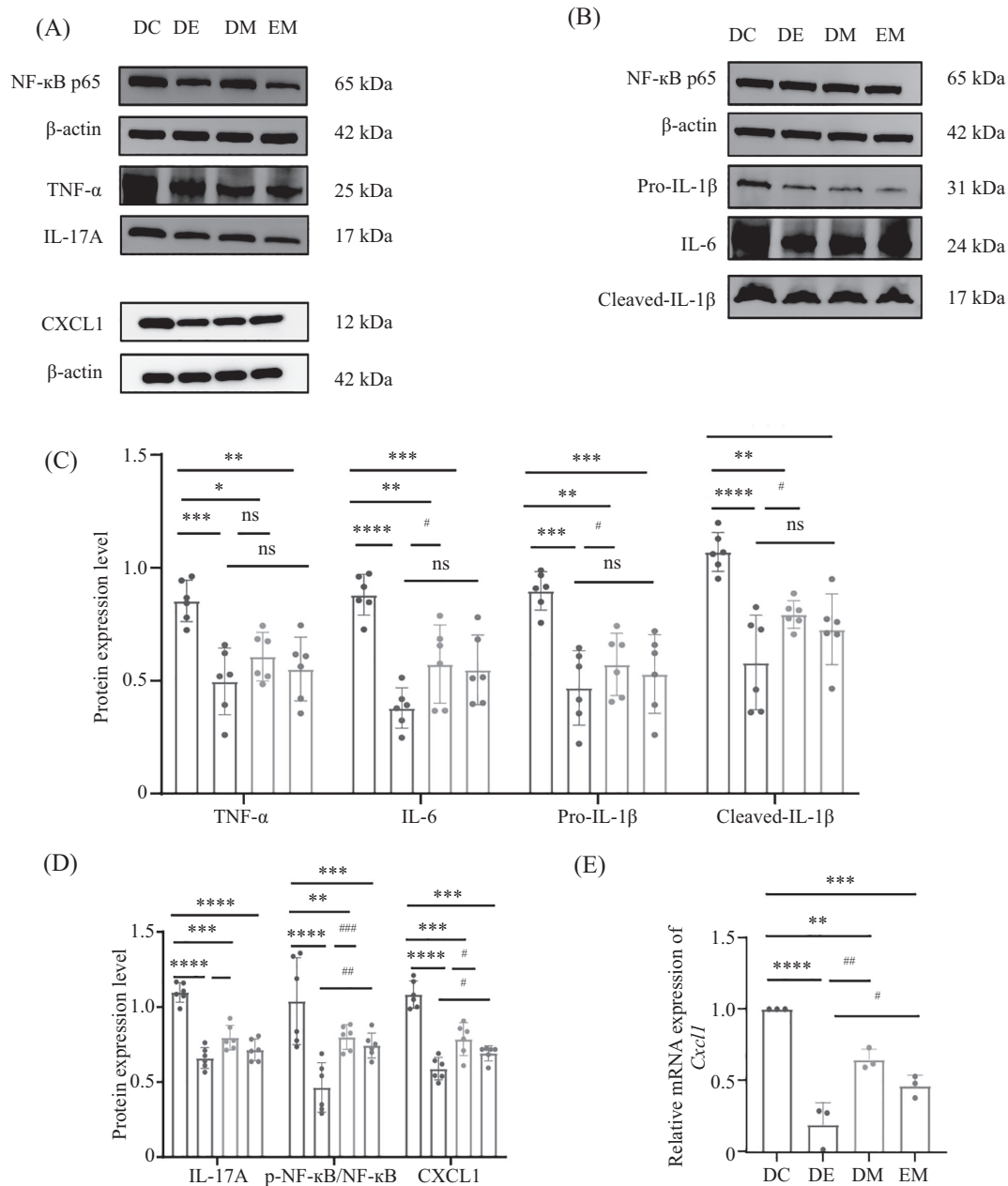
为进一步探究CXCL1对肝纤维化进展的调控作用, 将肝脏组织进行了Masson染色并对TGF- β 通路进行了蛋白检测。图6A显示, DC组出现肝细胞肿胀、排列紊乱, 汇管区及中央静脉周围可见些许蓝色胶原纤维沉积。经8周干预后DE组($P<0.000\ 1$)、DM组($P=0.001\ 7$)和EM组($P=0.000\ 4$)纤维沉积情况明显降低。

与DC组相比(图6B~图6E), DE和EM组TGF- β 1、 α -SMA、p-Smad2/3蛋白含量显著降低。DM组($P<0.001$)也表现相同的趋势, 即TGF- β 1、

α -SMA、p-Smad2/3蛋白表达下调, Smad2/3蛋白表达在各组之间无显著性差异。与DE组相比, DM组TGF- β 1、 α -SMA蛋白表达上调($P=0.008\ 4$; $P<0.01$)。EM组 α -SMA蛋白表达水平有增加趋势($P<0.001$), 其余指标无明显变化。结果表明, 运动和司美格鲁肽可能通过抑制CXCL1的表达来缓解肝脏的纤维化。

3 讨论

司美格鲁肽是一种长效GLP-1类似物, 经美国食品和药物管理局批准可用于治疗2型糖尿病^[27]。既往研究表明, 司美格鲁肽可通过减少肝脏脂质沉积、抑制肝脏炎症反应, 发挥显著的肝脏保护作用, 有效减轻MASLD肝脏病理损伤^[28]。高强度间歇训练等运动干预通过改善脂质代谢、调节肝脏免疫细胞浸润与巨噬细胞极化, 亦能减轻肝脏炎症甚至抑制纤维化发生^[20]。本研究发现, 无论是药物干预还



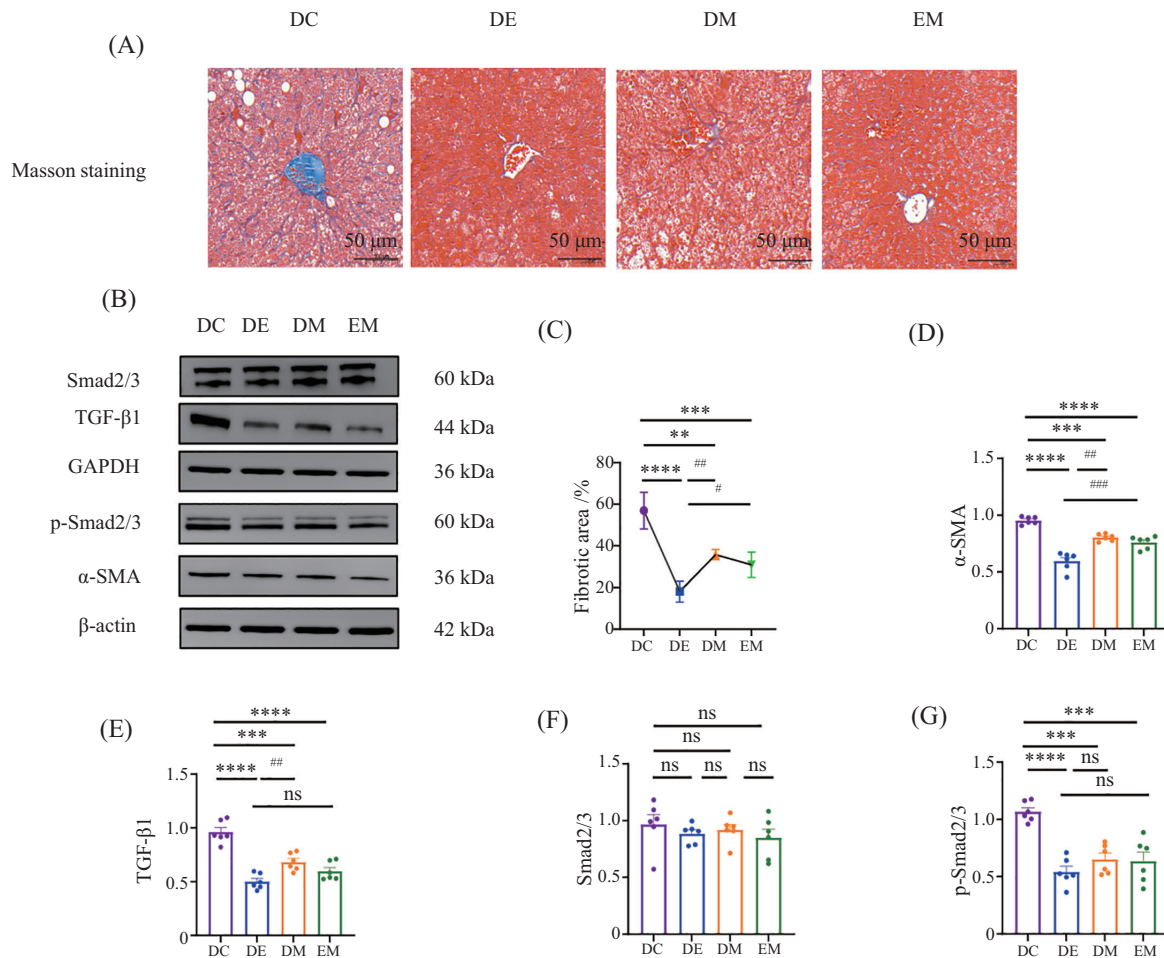
A、B: 蛋白表达条带; C: 炎症因子TNF- α 、IL-6、Cleaved-IL-1 β 、Pro-IL-1 β 的蛋白表达水平; D: IL-17A、p-NF- κ B/NF- κ B、CXCL1的蛋白表达水平; E: 肝组织*Cxcl1* mRNA水平。ns: $P>0.05$, * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; # $P<0.05$, ## $P<0.01$, ### $P<0.001$ 。n=6。
A,B: protein expression bands; C: protein expression of inflammatory factors TNF- α , IL-6, Cleaved-IL-1 β and Pro-IL-1 β ; D: protein expression of IL-17A, p-NF- κ B/NF- κ B and CXCL1; E: *Cxcl1* mRNA levels in liver tissues. ns: $P>0.05$, * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; # $P<0.05$, ## $P<0.01$, ### $P<0.001$ 。n=6。

图5 各组小鼠肝脏中炎症因子和IL-17通路蛋白的表达水平

Fig.5 Expression of inflammatory cytokines and IL-17 pathway-related proteins in the liver of mice from each group

是运动干预, 均能显著降低空腹血糖、摄食量、体质量及肝脏质量, 这与以往的研究保持一致^[29]。其一, 司美格鲁肽可通过刺激胰岛素分泌, 并通过延迟胃排空和促进饱腹感来抑制食欲^[30], 其二, 司美格鲁肽通过激活中枢神经系统的GLP-1受体来调控食物偏好, 减少能量摄入降低体质量^[31]。HIIT作为有

效的运动干预手段, 不仅能降低db/db小鼠体质量和血糖水平, 还能在一定程度上减少肝脏脂肪含量^[32]。单次HIIT干预也可有效降低2型糖尿病患者的空腹血糖水平, 具备良好的短期代谢改善效应^[33]。持续干预则具有更显著的代谢表现, 例如8周HIIT可降低肥胖男大学生体质量, 并引起血清瘦素、脂联素和



A: 各组小鼠肝脏Masson染色; B: 蛋白表达条带; C: Masson染色定量分析各组小鼠肝脏胶原纤维面积占比; D-G: α-SMA、TGF-β1、Smad2/3、p-Smad2/3的蛋白表达。ns: $P>0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; # $P<0.05$, ## $P<0.01$, ### $P<0.001$ 。n=6。

A: Masson's trichrome staining of liver tissue in each group; B: protein expression bands; C: quantitative analysis of hepatic collagen area fraction in mice of each group using Masson's trichrome staining; D-G: protein expression of α-SMA, TGF-β1, Smad2/3 and p-Smad2/3. ns: $P>0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$; # $P<0.05$, ## $P<0.01$, ### $P<0.001$ 。n=6。

图6 各组小鼠肝脏中纤维化相关蛋白的表达水平

Fig.6 Expression of fibrosis-related proteins in the liver of db/db mice in each group

鸢尾素水平的显著变化^[34]。12周的干预能有效改善T2DM患者体成分、心肺功能、血糖和血压等指标^[35]。

本研究转录组学揭示了司美格鲁肽和HIIT对代谢异常背景下肝脏炎症状态的系统性调控作用。与模型组相比,各干预方案均可不同程度逆转肝脏炎症相关基因的异常高表达。功能富集分析表明,筛选获得的差异表达基因主要富集于免疫应答、炎症反应及细胞因子介导的信号转导等生物学过程。在通路富集分析中,IL-17信号通路在不同干预组的差异表达基因中均呈现显著富集,提示IL-17轴可能是调控肝脏炎症的关键枢纽之一。既往研究表明,在2型糖尿病与肝癌等疾病的共同通路富集分析中,IL-17信号通路位列最显著富集通路之一,并与MASLD相关通路高度重叠^[36]。此外,本研究发现肝

脏炎症的改善在运动干预组中更为明显,这一结果与我们预期有所差异。HIIT已在多种动物模型中被证实能够显著缓解肝脏炎症,可通过特异性抑制肝脏中Toll样受体4和NF-κB信号通路的激活来缓解肝脏炎症^[37],通过AMPK/mTOR通路来减少肝脏蛋白质合成^[38]。特别是在NASH或肝损伤模型中,HIIT明显抑制巨噬细胞异常浸润且下调炎症基因的异常表达^[39]。运动被认为能够改善炎症组织的局部微环境,减少中性粒细胞的异常募集,这与CXCL1在炎症细胞迁移中的核心作用高度吻合。目前虽无文献证实semaglutide通过IL-17轴通路来缓解肝脏炎症,但其直接或间接通过NF-κB通路来改善肝脏炎症已被证实^[40]。司美格鲁肽可能通过直接作用于表达GLP-1受体的免疫细胞或通过血糖控制和体质量减轻等间

接机制来减轻炎症^[41], 其对肝脏局部炎症细胞募集及趋化因子网络的直接调控能力可能相对有限。此外, 运动干预在维持骨骼肌质量和功能方面具有独特优势, 而司美格鲁肽治疗常伴随体质量及肌肉量下降, 甚至可能影响骨骼肌完整性^[42]。骨骼肌作为重要的代谢与免疫调节器官, 可通过肌源性分泌因子介导与肝脏之间的代谢和炎症信号交流, 在维持肝脏炎症稳态中发挥关键的上游调节作用, 这可能是运动在抗炎效应上优于药物干预的重要原因之一^{—[43-44]}。

CXCL1作为强效的中性粒细胞趋化因子, 在NASH肝组织中显著上调^[45], 可大量募集中性粒细胞浸润肝脏, 释放炎症介质与促纤维化因子, 从而激活肝星状细胞并促进胶原沉积^[46]。本研究发现三种干预均可抑制IL-17信号通路, 并伴随CXCL1表达水平降低, 说明药物和运动干预可能切断了“IL-17/NF- κ B/CXCL1”的正反馈环路, 从而延缓肝脏炎症向纤维化阶段的进程。进一步而言, TGF- β /Smad通路是肝纤维化的核心驱动机制, 持续激活该通路可促进HSC向肌成纤维样表型转化^[47]。Western blot结果显示, 运动和药物干预均可下调 α -SMA、TGF- β 1及p-Smad2/3蛋白表达, 且Masson染色显示肝组织蓝色胶原沉积明显改善。然而, 整体呈现出“运动组>联合干预组>药物组”的效应, 与炎症改善的趋势一致。这可能是因为在炎症趋化信号被充分抑制的背景下, 促纤维化信号也同步减弱。IL-17/CXCL1轴可能与TGF- β 轴存在正向互作, 一旦前者被抑制, 后者也会被抑制。在肝脏疾病模型中, 日本学者Tomiga等^[48]发现, 规律的运动能显著逆转四氯化碳诱导的肝纤维化, 减轻肝脏病理损伤。运动训练降低了肝纤维化和与纤维化发生相关基因在糖尿病大鼠模型中mRNA的表达水平^[19]。临床研究中, HIIT显著下调血清肝纤维化标志物水平, 且整体改善率约为常规治疗组的5倍^[49]。相比之下, 司美格鲁肽虽具有明确的抗炎和改善肝脂肪变性的作用, 但其对肝纤维化的干预效果仍存在一定争议。Inia等^[50]证明司美格鲁肽能显著改善肥胖的*Ldlr*^{-/-}小鼠的肝脂肪变性和炎症, 仅能略微改善肝纤维化。Møllerhøj等^[51]同样报道, 在高脂肪、高果糖及胆固醇饮食诱导的MASH模型中, semaglutide虽减少肝脂肪变性, 但对纤维化无显著影响。机制研究表明, semaglutide通过靶向SIRT1/AMPK和TGF- β /Smad通路缓解小鼠肝脏纤维化^[52]。在临床方面, 已有研究显示, 司美格鲁

肽在严格筛选的MASH合并中重度纤维化患者中显示出抗纤维化潜力, 但需更多长期研究验证其组织学改善的持久性^[28]。结合我们的实验结果, 运动在抑制CXCL1及相关促纤维化信号方面具有更明显的优势, 联合干预虽改善趋势存在, 但不及单独运动效果。

HIIT与司美格鲁肽均可减少db/db小鼠肝脏脂质沉积、抑制肝脏炎症反应并减轻肝纤维化损伤, 其机制可能与抑制IL-17/NF- κ B/CXCL1信号通路相关。HIIT在改善MASLD肝脏脂质代谢、抑制炎症及纤维化进展方面效果更为显著, 为运动联合药物干预提升T2DM合并MASLD的协同保护效应提供了新的实验依据与理论支撑。

参考文献 (References)

- [1] Genitsaridi I, Salpea P, Salim A, et al. 11th edition of the IDF Diabetes Atlas: global, regional, and national diabetes prevalence estimates for 2024 and projections for 2050 [J]. The Lancet Diabetes & Endocrinology, 2026, 14(2): 149-156.
- [2] Harding J L, Pavkov M E, Magliano D J, et al. Global trends in diabetes complications: a review of current evidence [J]. Diabetologia, 2019, 62(1): 3-16.
- [3] Yasin A, Nguyen M, Sidhu A, et al. Liver and cardiovascular disease outcomes in metabolic syndrome and diabetic populations: bi-directional opportunities to multiply preventive strategies [J]. Diabetes Research and Clinical Practice, 2024, 211: 111650.
- [4] Kamalraj N, Sathishkumar M, Arunvignesh M, et al. Retrospective analysis (2009-2017) of factors associated with progression and regression of non-alcoholic fatty liver disease (hepatic steatosis) in patients with type 2 diabetes seen at a tertiary diabetes centre in Southern India [J]. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2021, 15(5): 102261.
- [5] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) [J]. Journal of Hepatology, 2024, 81(3): 492-542.
- [6] Wei S L, Wang L, Evans P C, et al. NAFLD and NASH: etiology, targets and emerging therapies [J]. Drug Discovery Today, 2024, 29(3): 103910.
- [7] Habibullah M, Jemmeh K, Ouda A, et al. Metabolic-associated fatty liver disease: a selective review of pathogenesis, diagnostic approaches, and therapeutic strategies [J]. Frontiers in Medicine, 2024, 11: 1291501.
- [8] Drożdż K, Nabrdalik K, Hajzler W, et al. Metabolic-associated fatty liver disease (MAFLD), diabetes, and cardiovascular disease: associations with fructose metabolism and gut microbiota [J]. Nutrients, 2021, 14(1): 103.
- [9] Nassir F. NAFLD: mechanisms, treatments, and biomarkers [J]. Biomolecules, 2022, 12(6): 824.
- [10] Mahapatra M K, Karuppasamy M, Sahoo B M. Therapeutic po-

- tential of semaglutide, a newer GLP-1 receptor agonist, in abating obesity, non-alcoholic steatohepatitis and neurodegenerative diseases: a narrative review [J]. *Pharmaceutical Research*, 2022, 39(6): 1233-1248.
- [11] Nauck M A, Quast D R, Wefers J, et al. GLP-1 receptor agonists in the treatment of type 2 diabetes-state-of-the-art [J]. *Molecular Metabolism*, 2021, 46: 101102.
- [12] Korda M. Semaglutide improves cardiovascular health independently of weight loss [J]. *Nature Cardiovascular Research*, 2024, 3(6): 615.
- [13] Chen T H, Hu E H, Chen D Y, et al. GLP-1 RAs and cardiovascular and kidney outcomes by body mass index in type 2 diabetes [J]. *JAMA Network Open*, 2025, 8(9): e2530952.
- [14] Hu Q, Zhang L, Tao Y T, et al. Semaglutide ameliorates hepatocyte steatosis in a cell co-culture system by downregulating the IRE1 α -XBP1-C/EBP α signaling pathway in macrophages [J]. *Pharmacology*, 2025, 110(1): 26-35.
- [15] Chen G, Banini B, Do A, et al. The independent effect of exercise on biopsy-proven non-alcoholic fatty liver disease: a systematic review [J]. *Clinical and Molecular Hepatology*, 2023, 29(S1): S319-S332.
- [16] Guarino M, Kumar P, Felsner A, et al. Exercise attenuates the transition from fatty liver to steatohepatitis and reduces tumor formation in mice [J]. *Cancers*, 2020, 12(6): 1407.
- [17] Kawanishi N, Yano H, Mizokami T, et al. Exercise training attenuates hepatic inflammation, fibrosis and macrophage infiltration during diet induced-obesity in mice [J]. *Brain, Behavior, and Immunity*, 2012, 26(6): 931-941.
- [18] Jeong J H, Lee Y R, Park H G, et al. The effects of either resveratrol or exercise on macrophage infiltration and switching from M1 to M2 in high fat diet mice [J]. *Journal of Exercise Nutrition and Biochemistry*, 2015, 19(2): 65-72.
- [19] Linden M A, Sheldon R D, Meers G M, et al. Aerobic exercise training in the treatment of non-alcoholic fatty liver disease related fibrosis [J]. *The Journal of Physiology*, 2016, 594(18): 5271-5284.
- [20] Houttu V, Bouts J, Vali Y, et al. Does aerobic exercise reduce NASH and liver fibrosis in patients with non-alcoholic fatty liver disease? A systematic literature review and meta-analysis [J]. *Frontiers in Endocrinology*, 2022, 13: 1032164.
- [21] van den Hoek A M, de Jong J C B C, Worms N, et al. Diet and exercise reduce pre-existing NASH and fibrosis and have additional beneficial effects on the vasculature, adipose tissue and skeletal muscle via organ-crosstalk [J]. *Metabolism*, 2021, 124: 154873.
- [22] Giles D, Moreno-Fernandez M, Divanovic S. IL-17 axis driven inflammation in non-alcoholic fatty liver disease progression [J]. *Current Drug Targets*, 2015, 16(12): 1315-1323.
- [23] Abdelnabi M N, Hassan G S, Shoukry N H. Role of the type 3 cytokines IL-17 and IL-22 in modulating metabolic dysfunction-associated steatotic liver disease [J]. *Frontiers in Immunology*, 2024, 15: 1437046.
- [24] Shi W P, Ju D, Li H, et al. CD147 promotes CXCL1 expression and modulates liver fibrogenesis [J]. *International Journal of Molecular Sciences*, 2018, 19(4): 1145.
- [25] Kavyani Z, Dehghan P, Khani M, et al. The effects of camelina sativa oil and high-intensity interval training on liver function and metabolic outcomes in male type 2 diabetic rats [J]. *Frontiers in Nutrition*, 2023, 10: 1102862.
- [26] Guo W J, Xu Z, Zou H X, et al. Discovery of ecnoglutide: a novel, long-acting, cAMP-biased glucagon-like peptide-1 (GLP-1) analog [J]. *Molecular Metabolism*, 2023, 75: 101762.
- [27] Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide [J]. *Journal of Medicinal Chemistry*, 2015, 58(18): 7370-7380.
- [28] Newsome P N, Sanyal A J, Engebretsen K A, et al. Semaglutide 2.4 mg in participants with metabolic dysfunction-associated steatohepatitis: baseline characteristics and design of the phase 3 essence trial [J]. *Alimentary Pharmacology & Therapeutics*, 2024, 60(11/12): 1525-1533.
- [29] Yu W J, Liu Y F, Le S L, et al. Multi-pathway-driven hepatic protection: Semaglutide combined with HIIT counteracts diabetic liver injury in db/db mice [J]. *Journal of Diabetes Investigation*, 2025, 16(12): 2145-2159.
- [30] Timms M, Bowen C, Steel R. Identification of semaglutide use through detection of U6 and U7 metabolites in human urine [J]. *Analytical and Bioanalytical Chemistry*, 2026, 418(4): 1115-1124.
- [31] Gabery S, Salinas C G, Paulsen S J, et al. Semaglutide lowers body weight in rodents via distributed neural pathways [J]. *JCI Insight*, 2020, 5(6): e133429.
- [32] Zheng L F, Qin R T, Rao Z J, et al. High-intensity interval training induces renal injury and fibrosis in type 2 diabetic mice [J]. *Life Sciences*, 2023, 324: 121740.
- [33] Terada T, Wilson B J, Myette-Côté E, et al. Targeting specific interstitial glycemic parameters with high-intensity interval exercise and fasted-state exercise in type 2 diabetes [J]. *Metabolism*, 2016, 65(5): 599-608.
- [34] 赵睿, 周伟, 赵延敏, 等. 高强度间歇训练对肥胖男大学生脂肪因子的影响[J]. *中国学校卫生*, 2024, 45(7): 960-964.
Zhao R, Zhou W, Zhao Y M. Effects of high-intensity interval training on adipokines in obese male college students [J]. *Chinese Journal of School Health*, 2024, 45(7): 960-964.
- [35] Li J, Cheng W, Ma H F. A comparative study of health efficacy indicators in subjects with T2DM applying power cycling to 12 weeks of low-volume high-intensity interval training and moderate-intensity continuous training [J]. *Journal of Diabetes Research*, 2022, 2022: 9273830.
- [36] Nayan S I, Rahman M H, Hasan Md M, et al. Network based approach to identify interactions between type 2 diabetes and cancer comorbidities [J]. *Life Sciences*, 2023, 335: 122244.
- [37] Malheiro L F L, Oliveira C A, Portela F S, et al. High-intensity interval training alleviates liver inflammation by regulating the TLR4/NF- κ B signaling pathway and M1/M2 macrophage balance in female rats with cisplatin hepatotoxicity [J]. *Biochemical and Biophysical Research Communications*, 2024, 733: 150712.
- [38] Wang Y, Guo Y F, Xu Y Y, et al. HIIT ameliorates inflammation and lipid metabolism by regulating macrophage polarization and mitochondrial dynamics in the liver of type 2 diabetes mellitus mice [J]. *Metabolites*, 2022, 13(1): 14.
- [39] Fredrickson G, Barrow F, Dietsche K, et al. Exercise of high intensity ameliorates hepatic inflammation and the progression of NASH [J]. *Molecular Metabolism*, 2021, 53: 101270.
- [40] El Sayed N F, Baraka S A, El-Mokadem B M, et al. Exploring

- novel protective role of semaglutide in 5-fluorouracil-induced hepatotoxicity: insights into phosphorylated CREB, PINK1/Parkin-mediated mitophagy, and NF- κ B/NLRP3 pathways [J]. *The Journal of Pharmacology and Experimental Therapeutics*, 2025, 392(8): 103629.
- [41] Lee Y S, Jun H S. Anti-inflammatory effects of GLP-1-based therapies beyond glucose control [J]. *Mediators of Inflammation*, 2016, 2016(1): 1-11.
- [42] Ren Q J, Zhi L, Liu H F. Semaglutide therapy and accelerated sarcopenia in older adults with type 2 diabetes: a 24-month retrospective cohort study [J]. *Drug Design, Development and Therapy*, 2025, 19: 5645-5652.
- [43] Codella R, Senesi P, Luzi L. GLP-1 agonists and exercise: the future of lifestyle prioritization [J]. *Frontiers in Clinical Diabetes and Healthcare*, 2025, 6: 1720794.
- [44] Guo S S, Feng Y H, Zhu X P, et al. Metabolic crosstalk between skeletal muscle cells and liver through IRF4-FSTL1 in nonalcoholic steatohepatitis [J]. *Nature Communications*, 2023, 14(1): 6047.
- [45] Semba T, Nishimura M, Nishimura S, et al. The FLS (fatty liver shionogi) mouse reveals local expressions of lipocalin-2, CXCL1 and CXCL9 in the liver with non-alcoholic steatohepatitis [J]. *BMC Gastroenterology*, 2013, 13(1): 120.
- [46] Amatya N, Garg A V, Gaffen S L. IL-17 signaling: the yin and the yang [J]. *Trends in Immunology*, 2017, 38(5): 310-322.
- [47] Wang W L, Gao Y L, Chen Y Z, et al. TGF- β inhibitors: the future for prevention and treatment of liver fibrosis? [J]. *Frontiers in Immunology*, 2025, 16: 1583616.
- [48] Tomiga Y, Tanaka K, Kusuyama J, et al. Exercise training ameliorates carbon tetrachloride-induced liver fibrosis and anxiety-like behaviors [J]. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 2024, 327(6): G850-G860.
- [49] Harris S J, Smith N, Hummer B, et al. Exercise training improves serum biomarkers of liver fibroinflammation in patients with metabolic dysfunction-associated steatohepatitis [J]. *Liver International*, 2024, 44(2): 532-540.
- [50] Inia J A, Stokman G, Morrison M C, et al. Semaglutide has beneficial effects on non-alcoholic steatohepatitis in Ldlr^{-/-}.Leiden mice [J]. *International Journal of Molecular Sciences*, 2023, 24(10): 8494.
- [51] Møllerhøj M B, Veidal S S, Thrane K T, et al. Hepatoprotective effects of semaglutide, lanifibranor and dietary intervention in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH [J]. *Clinical and Translational Science*, 2022, 15(5): 1167-1186.
- [52] Hawary O A, Wadie W, El-Said Y A M, et al. Repurposing of semaglutide by targeting SIRT1 and TGF- β /Smad signaling in hepatic fibrosis [J]. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 2025, 399(3): 4413-4425.