

• 述 评 •

多系统交互网络视角下儿童肥胖相关代谢性疾病的免疫-代谢-力学三维机制解析

郭锡熔

上海市同仁医院, 上海交通大学医学院附属同仁医院, 虹桥国际医学研究院, 上海 200336

摘要: 儿童肥胖及相关代谢性疾病(如胰岛素抵抗、脂代谢紊乱、代谢相关脂肪性肝病等)已成为重要公共卫生问题。既往研究往往聚焦于单一器官或组织层面的改变,难以解析肥胖进程中多组织器官的动态变化。儿童肥胖相关代谢紊乱本质上是脂肪组织功能障碍引发的、涉及免疫系统失调和代谢稳态失衡等多系统深度交互的复杂网络性疾病。本文系统综述了当前儿童肥胖与代谢性疾病之间关联机制的研究进展,重点聚焦三大病理路径:免疫细胞介导的慢性炎症、代谢物积累与代谢重编程、以及脂肪组织生物力学微环境异常。研究显示,在肥胖状态下,T细胞、B细胞及巨噬细胞在脂肪组织中活性改变,构建免疫-代谢的双向反馈回路;支链氨基酸和非酯化脂肪酸等代谢物可干扰胰岛素信号传导,引发胰岛素抵抗;而细胞外基质硬化及力学应激增强则进一步激活炎症通路,形成“免疫-代谢-基质”复合网络。儿童肥胖相关代谢异常具有早发、多器官、长期遗留等特点。未来应加强多组学技术整合与多系统互作机制研究,推动个体化干预策略的临床转化,以改善儿童肥胖相关代谢性疾病的防治效果。

关键词: 儿童肥胖; 代谢性疾病; 免疫细胞; 代谢重编程; 细胞生物力学

中图分类号:R179 文献标识码:A 文章编号:1008-6579(2025)10-1052-04 doi:10.11852/zgetbjzz2025-0969

Three-dimensional mechanisms of immune-metabolic-mechanical interactions in metabolic diseases associated with childhood obesity from the perspective of multi-system interaction networks

GUO Xirong

Hongqiao International Institute of Medicine, Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200336, China

Abstract: Childhood obesity and its associated metabolic diseases (e.g., insulin resistance, dyslipidemia, metabolic dysfunction-associated fatty liver disease, etc.) have emerged as a significant public health concern. Previous studies often focused on changes at the single organ or tissue level, making it challenging to elucidate the dynamic changes across multiple tissues and organs during the progression of obesity. Metabolic disorders related to childhood obesity are essentially complex network diseases initiated by the dysfunction or collapse of adipose tissue function, involving deep interactions among multiple systems such as immune system dysregulation and the collapse of metabolic homeostasis. This study systematically reviews current research progress on the mechanisms underlying the association between childhood obesity and metabolic diseases, with a focus on three key pathological pathways: chronic inflammation mediated by immune cells, metabolite accumulation and metabolic reprogramming, and abnormal changes in adipose tissue biomechanics microenvironment. It is reported that T cells, B cells, and macrophages exhibit altered activity in adipose tissue with obesity, establishing a bidirectional feedback loop between immunity and metabolism. Metabolites such as branched-chain amino acids and non-esterified fatty acids can interfere with insulin signaling, inducing insulin resistance. Besides, extracellular matrix stiffening and increased mechanical stress further activate inflammatory pathways, forming an immune-metabolic-matrix composite network. Metabolic abnormalities associated with childhood obesity are characterized by early onset, multi-organ involvement, and long-term persistence. Future research should enhance the integration of multi-omics technologies with investigations into the mechanisms of multi-system interactions, promoting the clinical translation of personalized intervention strategies, and thereby improving the prevention and treatment outcomes of childhood obesity-related metabolic diseases.

Keywords: childhood obesity; metabolic diseases; immune cells; metabolic reprogramming; cellular biomechanics

基金项目:国家重点研发计划(2021YFC2701900, 2021YFC2701903);国家自然科学基金(82170869)

作者简介:郭锡熔(1966—),男,主任医师,博士生导师,主要研究方向为儿童肥胖与代谢综合征。

肥胖已成为全球最紧迫的公共卫生问题之一。儿童肥胖及相关代谢性疾病(如 2 型糖尿病、代谢相关脂肪性肝病、代谢综合征等)发病率居高不下,且缺乏有效的早期预警、干预手段。数据显示:美国 2008—2023 年儿童肥胖患病率显著增加,其中 84.6% 患代谢相关脂肪性肝病,53.8% 患代谢综合征,且患病风险随肥胖等级呈剂量效应增长^[1]。肥胖发生的本质是能量平衡失调,是基底体相关蛋白复合体(Bardet-Biedl syndrome protein complex, BBSome)破坏、代谢相关脂肪性肝病等共病的发生基础^[2]。既往研究重点探讨营养、行为、运动、心理等诱发儿童肥胖的主要因素,尽管进行了孕期因素^[3]、表观遗传的多哈理论^[4]、母乳或饮食与肠道菌群^[5]、行为疗法或运动疗法^[6]、跨物种传输^[7]等跨界初步研究,仍需在原先独立研究单个组织或脏器(如肝脏、脂肪组织、胰岛组织等)变化的基础上作新的思考。近年来,研究视角已从单一器官扩展至多系统交互网络,免疫细胞浸润、代谢重编程及细胞生物力学微环境异常等新兴机制逐步成为研究热点。本文围绕儿童肥胖与代谢性疾病的核心关联,从免疫微环境的调控作用、代谢物与细胞功能的交互及生物力学微环境影响三个维度展开系统综述,为儿童肥胖及相关代谢性疾病的防治提供理论依据与研究指导。

1 免疫细胞联动肥胖及相关代谢性疾病

1.1 T 细胞联动肥胖及相关代谢性疾病 在肥胖进展过程中,T 细胞的异常激活被认为是脂肪组织炎症反应的早期驱动因素。Nishimura 等^[8]研究发现,高脂饮食干预仅 5 周,T 细胞即开始显著扩增,其浸润程度早于巨噬细胞的大量聚集(通常在第 10 周左右)。其中,CD8⁺ 细胞毒性 T 细胞可通过分泌干扰素 γ (IFN- γ)破坏脂肪细胞的胰岛素敏感性,抑制葡萄糖转运蛋白 4、胰岛素受体底物 1 和过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ , PPAR γ)等关键因子的表达,并通过激活 STAT1 通路诱导巨噬细胞向促炎表型转化。此外,调节性 T 细胞(Treg)通过分泌 IL-10 和 TGF- β 维持脂肪组织免疫稳态,其在非肥胖个体内脏脂肪中显著富集;而肥胖状态下 Treg 因 FOXP3 基因超甲基化发生耗竭,削弱对炎症环境的抑制功能^[9]。

1.2 B 细胞联动肥胖及相关代谢性疾病 近年来,B 细胞在代谢炎症中的角色逐渐受到重视。B 细胞通过表达 Toll 样受体(toll like receptors, TLRs)识

别内源性脂肪酸或肠道菌群代谢产物,从而激活 NF- κ B 等炎症通路。例如,TLR4 介导的信号可上调 MHC-II 分子表达,增强抗原递呈能力;TLR2 激活则促进 B 细胞增殖与 IgG 分泌,增强自身免疫反应^[10-12]。此外,TLR9 还可识别微生物 DNA 片段(如 CpG-DNA),进一步刺激 B 细胞分泌促炎因子,形成肠道菌群与免疫激活之间的正反馈机制。研究发现,肥胖儿童肠道中 IgM 结合菌群的比例显著升高,且可通过粪菌移植诱导无菌小鼠出现体重增加与糖耐量下降表型^[13-14]。同时,具有促炎特征的 T-bet⁺ B 细胞在肥胖个体中大量积聚,而分泌 IL-10 的保护性 B-1 细胞功能则被抑制,进一步加剧胰岛素抵抗^[15]。这种亚群失衡导致“代谢记忆”效应——表观遗传修饰持续影响代谢表型,即使体重恢复后炎症仍难以消退。

1.3 巨噬细胞联动肥胖及相关代谢性疾病 脂肪组织是肥胖最早影响的靶器官,其中脂肪组织巨噬细胞(adipose tissue macrophages, ATMs)的异常活化是驱动系统性代谢紊乱的重要起始环节。在健康状态下,其巨噬细胞多为 M2 型,具有抗炎特性,并通过分泌 Arg-1、IL-10 等维持代谢稳态^[16]。而在肥胖条件下,过度脂质沉积引发局部缺氧,进而激活 HIF-1 α 信号通路,诱导巨噬细胞向促炎 M1 型极化。此类 M1 型细胞高表达 CD11c、iNOS 和 TNF- α 等因子,在组织内建立慢性炎症环境,加剧胰岛素抵抗的发生^[17]。

免疫细胞在儿童肥胖及相关代谢性疾病进程中不仅充当炎症反应的发起者,更通过细胞因子分泌和表型塑造持续调节脂肪组织微环境,从而在代谢紊乱发展中发挥关键作用。T 细胞启动、B 细胞介导、巨噬细胞维持炎症状态,三者级联反应构成免疫失衡的核心通路。

2 代谢物与代谢重编程联动肥胖及相关代谢性疾病

2.1 代谢物联动肥胖及相关代谢性疾病 内脏脂肪组织在肥胖状态下显著扩张,伴随脂解活性升高,释放大量非酯化脂肪酸进入循环,形成“脂质溢出”现象。这些脂质在肝脏、肌肉等非脂肪组织中异常沉积,激活 PKC θ 、JNK 等信号通路,干扰胰岛素信号转导,诱发系统性胰岛素抵抗(insulin resistance, IR)^[18]。伴随 IR 的代偿性高胰岛素血症进一步促进肝脏极低密度脂蛋白合成,引发高甘油三酯血症^[19]。饱和脂肪酸,如棕榈酸,可通过 TLR4-NL- RP3 炎症小体途径增强脂肪组织炎症反应^[20],而单不饱和脂肪酸如油酸则通过抑制 NLRP3 激活、增

强 PPAR γ 信号,维持脂肪组织代谢稳态^[21]。

氨基酸代谢紊乱是连接肥胖与脂肪肝的重要桥梁。支链氨基酸 (branched chain amino acid, BCAAs) 的积累激活哺乳动物雷帕霉素靶蛋白复合物 1 (mTORC1) 信号^[22],尤其在骨骼肌中通过 mTORC1/S6K1 通路抑制 PI3K/Akt 介导的胰岛素信号,降低葡萄糖摄取效率^[23]。此外,BCAA 代谢中间产物如酰基肉碱和二酰甘油的积聚可引发线粒体负荷增加,形成脂毒性微环境,进一步损害胰岛素敏感性^[24]。

2.2 代谢重编程联动肥胖及相关代谢性疾病 线粒体功能紊乱构成代谢失衡的起点。肥胖状态下,细胞内线粒体超微结构受损,表现为嵴断裂、膜电位下降和活性氧 (reactive oxygen species, ROS) 积聚,导致细胞代谢偏好糖酵解,ATP 合成效率显著下降。这一能量危机在肥胖儿童的气道上皮细胞中尤为明显,引发胰岛 β 细胞功能受损,加速胰岛素抵抗向 2 型糖尿病演变^[25-26]。表观遗传调控机制进一步维持代谢异常状态,肥胖状态下 TET 酶介导的羟甲基化可改变关键代谢基因的转录活性。例如,SLC25A4 启动子羟甲基化增强,促进线粒体载体蛋白过表达,而 ECI1 低羟甲基化则抑制脂肪酸 β 氧化通路,导致脂质在肝脏等器官异常积聚。研究表明,TET 酶抑制剂可改善肥胖来源干细胞的线粒体功能与 ATP 生成^[27-29]。此外,脂肪因子失衡放大炎症与代谢紊乱。肥胖儿童常合并瘦素抵抗(循环水平升高但信号传导受阻),破坏 AMPK 介导的脂肪酸氧化,并通过激活 JAK/STAT 及降低脂联素分泌,协同 IL-6、TNF- α 等因子经 NF- κ B 通路诱导巨噬细胞向 M1 型极化,最终形成以慢性低度炎症为特征的代谢性炎症状态^[30-31]。

3 细胞生物力联动肥胖及相关代谢性疾病

细胞生物力可作为免疫与代谢联动的承接点。在肥胖状态下,脂肪组织细胞外基质 (extracellular matrix, ECM) 发生重构,主要表现为 I 型和 III 型胶原蛋白过度沉积及交联增强,导致基质硬化和弹性模量升高^[32]。ECM 力学特性改变会激活脂肪组织内巨噬细胞的模式识别受体 (如 TLR4、TLR9),进而启动下游 NF- κ B 通路,引发促炎因子如 TNF- α 、IL-6 的持续分泌,形成低度慢性炎症微环境^[33]。炎症状态进一步损伤脂滴力学稳定性。Perilipin 家族蛋白 (如 PLIN1) 表达下降,导致脂滴表面张力调节能力下降,使其形态粘滞且不稳定,脂解酶功能受限,引发游离脂肪酸和神经酰胺等脂毒性分子异常

积聚^[34]。此类脂毒性代谢产物可进一步激活 NLRP3 炎症小体,引发促炎级联反应,并抑制线粒体 β -氧化酶功能,阻断脂肪酸氧化通路,造成 ROS 大量生成^[35]。ROS 的积聚不仅损伤线粒体功能,还通过稳定 HIF-1 α 蛋白表达,诱导糖酵解相关酶活性上升,引导细胞代谢从氧化磷酸化转向有氧糖酵解,即“Warburg 效应”。乳酸积累造成组织酸化,而低 pH 可进一步激活基质金属蛋白酶 (matrix metalloproteinases, MMPs),促使 ECM 降解与再沉积循环。

免疫细胞分泌细胞因子参与力学-代谢联动病理进程。巨噬细胞分泌 IL-6 可通过 JAK-STAT3 通路抑制脂联素启动子活性,降低脂联素表达,间接抑制 AMPK 信号通路,从而下调脂肪酸氧化关键酶 (如 CPT1、ACOX1)^[36]。此外,CD8⁺ T 细胞释放的 IFN- γ 可激活 STAT1-IDO 通路,加速色氨酸代谢为犬尿氨酸,后者通过激活脂肪祖细胞中芳香烃受体信号,诱导其向成纤维脂肪祖细胞 (fibro/adipogenic progenitors, FAPs) 分化^[37]。这些 FAPs 细胞不仅分泌大量胶原与纤连蛋白,加重组织硬化,还与巨噬细胞、成熟脂肪细胞协同,构成“免疫-代谢-基质”三重互作网络,加剧胰岛素抵抗与组织纤维化。

儿童肥胖作为代谢性疾病的重要前驱状态,具有显著的早发、多器官、长期遗留等特征。免疫细胞可联动肥胖及相关代谢性疾病,CD8⁺ T 细胞分泌 IFN- γ 诱导巨噬细胞 M1 极化,B 细胞 TLR4/TLR9 激活加剧炎症,Treg 因 FOXP3 甲基化耗竭,形成慢性炎症微环境。代谢重编程可作为交互纽带,肝脏 SREBP-1c 过表达致脂质合成亢进,脂肪 UCP1 表达下降引发产热障碍,骨骼肌 BCAAs 代谢异常抑制胰岛素信号,形成多器官代谢紊乱。生物力学信号可作为联动承接点,脂肪组织胶原沉积致基质硬化,激活整合素 $\alpha\gamma\beta 3$ /FAK 通路,并通过 YAP/TAZ 诱导 MMPs,加剧 ECM 降解-再沉积循环。肥胖及其共病调控通路复杂,既往研究采用二元论研究方法,在未来,三元论及多元论成为新的研究趋势。不仅需要在整体水平进行研究,更需要在类器官基础上,借助小室设计,开展复合性研究。随着研究逐步深入,通过解析多器官与微生态多系统的动态互作关系及基础与临床的交叉融合,最终实现从早期预测到精准靶点控制的全流程优化,为儿童健康成长提供科学保障。

参考文献

- [1] Munte E, Zhang X, Khurana A, et al. Prevalence of extremely severe obesity and metabolic dysfunction among US

- children and adolescents[J]. JAMA Netw Open, 2025, 8(7): e2521170.
- [2] Guo DF, Lin Z, Wu Y, et al. The BBSome in POMC and AgRP neurons is necessary for body weight regulation and sorting of metabolic receptors[J]. Diabetes, 2019, 68(8): 1591-1603.
- [3] Muglia LJ, Benhalima K, Tong S, et al. Maternal factors during pregnancy influencing maternal, fetal, and childhood outcomes[J]. BMC Med, 2022, 20(1): 418.
- [4] Hoffman DJ, Powell TL, Barrett ES, et al. Developmental origins of metabolic diseases[J]. Physiol Rev, 2021, 101(3): 739-795.
- [5] Du W, Zou ZP, Ye BC, et al. Gut microbiota and associated metabolites: Key players in high-fat diet-induced chronic diseases[J]. Gut Microbes, 2025, 17(1): 2494703.
- [6] Grilo CM, Lydecker JA, Fineberg SK, et al. Naltrexone-bupropion and behavior therapy, alone and combined, for binge-eating disorder: Randomized double-blind placebo-controlled trial[J]. Am J Psychiatry, 2022, 179(12): 927-937.
- [7] Aquilano K, Ceci V, Gismondi A, et al. Adipocyte metabolism is improved by TNF receptor-targeting small RNAs identified from dried nuts[J]. Commun Biol, 2019, 2: 317.
- [8] Nishimura S, Manabe I, Nagasaki M, et al. CD8⁺ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity[J]. Nat Med, 2009, 15(8): 914-920.
- [9] Yu W, Li C, Zhang D, et al. Advances in T cells based on inflammation in metabolic diseases [J]. Cells, 2022, 11(22): 3554.
- [10] Rogers J, Hakki A, Perkins I, et al. Legionella pneumophila infection up-regulates dendritic cell Toll-like receptor 2 (TLR2)/TLR4 expression and key maturation markers [J]. Infect Immun, 2007, 75(6): 3205-3208.
- [11] Winer DA, Winer S, Shen L, et al. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies[J]. Nat Med, 2011, 17(5): 610-617.
- [12] DeFuria J, Belkina AC, Jagannathan-Bogdan M, et al. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile[J]. Proc Natl Acad Sci U S A, 2013, 110(13): 5133-5138.
- [13] Pearson JA, Ding H, Hu C, et al. IgM-associated gut bacteria in obesity and type 2 diabetes in C57BL/6 mice and humans[J]. Diabetologia, 2022, 65(8): 1398-1411.
- [14] Harmon DB, Srikakulapu P, Kaplan JL, et al. Protective role for B-1b B cells and IgM in obesity-associated inflammation, glucose intolerance, and insulin resistance[J]. Arterioscler Thromb Vasc Biol, 2016, 36(4): 682-691.
- [15] Samiea A, Celis G, Yadav R, et al. B cells in non-lymphoid tissues[J]. Nat Rev Immunol, 2025, 25(7): 483-496.
- [16] Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization [J]. J Clin Invest, 2007, 117(1): 175-184.
- [17] Liu H, Wang P, Xu F, et al. The hydrophilic metabolite UMP alleviates obesity traits through a HIF2 α -ACER2-ceramide signaling axis [J]. Adv Sci, 2024, 11(21): e2309525.
- [18] Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome—an allostatic perspective[J]. Biochim Biophys Acta, 2010, 1801(3): 338-349.
- [19] Corrigendum for “Assessment of β cell mass and function by AIRmax and intravenous glucose in high-risk subjects for type 1 diabetes”[J]. J Clin Endocrinol Metab, 2018, 103(4): 1653.
- [20] Wen H, Gris D, Lei Y, et al. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling[J]. Nat Immunol, 2011, 12(5): 408-415.
- [21] Finucane OM, Lyons CL, Murphy AM, et al. Monounsaturated fatty acid-enriched high-fat diets impede adipose NLRP3 inflammasome-mediated IL-1 β secretion and insulin resistance despite obesity [J]. Diabetes, 2015, 64(6): 2116-2128.
- [22] Lynch CJ, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance[J]. Nat Rev Endocrinol, 2014, 10(12): 723-736.
- [23] Hernández-Alvarez MI, Díaz-Ramos A, Berdasco M, et al. Early-onset and classical forms of type 2 diabetes show impaired expression of genes involved in muscle branched-chain amino acids metabolism[J]. Sci Rep, 2017, 7(1): 13850.
- [24] White PJ, Lapworth AL, An J, et al. Branched-chain amino acid restriction in Zucker-fatty rats improves muscle insulin sensitivity by enhancing efficiency of fatty acid oxidation and acyl-glycine export[J]. Mol Metab, 2016, 5(7): 538-551.
- [25] Eirin A, Thaler R, Glastetter LM, et al. Obesity-driven mitochondrial dysfunction in human adipose tissue-derived mesenchymal stem/stromal cells involves epigenetic changes[J]. Cell Death Dis, 2024, 15(6): 387.
- [26] Hartsoe P, Holguin F, Chu HW. Mitochondrial dysfunction and metabolic reprogramming in obesity and asthma [J]. Int J Mol Sci, 2024, 25(5): 2944.
- [27] Zhou T, Pan J, Xu K, et al. Single-cell transcriptomics in MI identify Slc25a4 as a new modulator of mitochondrial malfunction and apoptosis-associated cardiomyocyte sub-cluster[J]. Sci Rep, 2024, 14(1): 9274.
- [28] González-Domínguez Á, Belmonte T, González-Domínguez R. Childhood obesity, metabolic syndrome, and oxidative stress: microRNAs go on stage[J]. Rev Endocr Metab Disord, 2023, 24(6): 1147-1164.
- [29] Chen ZJ, Das SS, Kar A, et al. Single-cell DNA methylome and 3D genome atlas of human subcutaneous adipose tissue [J]. Nat Genet, 2025; 1-12.
- [30] Badr M, El-Rabaa G, Freiha M, et al. Endocrine consequences of childhood obesity: A narrative review[J]. Front Endocrinol, 2025, 16: 1584861.

- chain amino acids deprivation on insulin sensitivity and glucose metabolism in mice[J]. *Metabolism*, 2014, 63(6): 841-850.
- [13] Selen ES, Wolfgang MJ. mTORC1 activation is not sufficient to suppress hepatic PPAR α signaling or ketogenesis[J]. *J Biol Chem*, 2021, 297(1):100884.
- [14] Xu X, Hu J, McGrath BC, et al. GCN2 regulates the CCAAT enhancer binding protein beta and hepatic gluconeogenesis[J]. *Am J Physiol Endocrinol Metab*, 2013, 305(8):e1007-e1017.
- [15] Zhao C, Liu L, Liu Q, et al. Fibroblast growth factor 21 is required for the therapeutic effects of lactobacillus rhamnosus GG against fructose-induced fatty liver in mice[J]. *Mol Metab*, 2019, 29:145-157.
- [16] Pi D, Liang Z, Pan J, et al. Tanshinone IIA inhibits the endoplasmic reticulum stress-induced unfolded protein response by activating the PPAR α /FGF21 axis to ameliorate nonalcoholic steatohepatitis [J]. *Antioxidants (Basel)*, 2024, 13(9):1026.
- [17] Ye X, Sun P, Lao S, et al. Fgf21-Dubosiella axis mediates the protective effects of exercise against NAFLD development[J]. *Life Sci*, 2023, 334:122231.
- [18] Yu D, Richardson NE, Green CL, et al. The adverse metabolic effects of branched-chain amino acids are mediated by isoleucine and valine[J]. *Cell Metab*, 2021, 33(5):905-922. e6.
- [19] Ma N, Wang YK, Xu S, et al. PDPF alleviates hepatic steatosis through inhibition of mTOR signaling [J]. *Nat Commun*, 2021, 12(1): 3059.
- [20] Yan XL, Pan YH, Fan RZ, et al. discovery of the first rapTOR (Regulatory-Associated Protein of mTOR) inhibitor as a new type of antiadipogenic agent[J]. *J Med Chem*, 2023, 66(8):5839-5858.
- [21] Mazor KM, Stipanuk MH. GCN2-and eIF2 α -phosphorylation-independent, but ATF4-dependent, induction of CARE-containing genes in methionine-deficient cells[J]. *Amino Acids*, 2016, 48(12):2831-2842.
- [22] Liu S, Yuan J, Yue W, et al. GCN2 deficiency protects against high fat diet induced hepatic steatosis and insulin resistance in mice[J]. *Biochim Biophys Acta Mol Basis Dis*, 2018, 1864(10):3257-3267.
- [23] Yuan J, Li F, Shen X, et al. Genetic and pharmacological inhibition of GCN2 ameliorates hyperglycemia and insulin resistance in type 2 diabetic mice[J]. *Antioxidants (Basel)*, 2022, 11(8):1584.
- [24] Batch BC, Shah SH, Newgard CB, et al. Branched chain amino acids are novel biomarkers for discrimination of metabolic wellness[J]. *Metabolism*, 2013, 62(7):961-969.
- [25] Ni Y, Qian L, Siliceo SL, et al. Resistant starch decreases intrahepatic triglycerides in patients with NAFLD via gut microbiome alterations[J]. *Cell Metab*, 2023, 35(9):1530-1547. e8.
- [26] Beppu T, Nitta H, Hayashi H, et al. Effect of branched-chain amino acid supplementation on functional liver regeneration in patients undergoing portal vein embolization and sequential hepatectomy: A randomized controlled trial[J]. *J Gastroenterol*, 2015, 50(12):1197-205.
- [27] Magkos F, Bradley D, Schweitzer GG, et al. Effect of Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding on branched-chain amino acid metabolism[J]. *Diabetes*, 2013, 62(8):2757-2761.
- [28] Yu G, Wang J, Liu Y, et al. Metabolic perturbations in pregnant rats exposed to low-dose perfluorooctanesulfonic acid: An integrated multi-omics analysis[J]. *Environ Int*, 2023, 173:107851.
- [29] Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors [J]. *Nat Aging*, 2023, 3(6): 642-660.
- [30] Krishnan S, Ding Y, Saedi N, et al. Gut microbiota-derived tryptophan metabolites modulate inflammatory response in hepatocytes and macrophages[J]. *Cell Rep*, 2018, 23(4): 1099-1111.
- [31] Zhou M, Shao J, Wu CY, et al. Targeting BCAA catabolism to treat obesity-associated insulin resistance[J]. *Diabetes*, 2019, 68(9):1730-1746.
- [32] Tedesco L, Corsetti G, Ruocco C, et al. A specific amino acid formula prevents alcoholic liver disease in rodents[J]. *Am J Physiol Gastrointest Liver Physiol*, 2018, 314(5): G566-G582.
- [33] Ge MK, Zhang C, Zhang N, et al. The tRNA-GCN2-FBXO22-axis-mediated mTOR ubiquitination senses amino acid insufficiency[J]. *Cell Metab*, 2023, 35(12):2216-2230. e8.

收稿日期:2025-03-27 修回日期:2025-07-19 本文编辑:王悦

(上接第 1055 页)

- [31] Wen X, Zhang B, Wu B, et al. Signaling pathways in obesity: Mechanisms and therapeutic interventions[J]. *Signal Transduct Target Ther*, 2022, 7(1): 298.
- [32] Musale V, Wasserman DH, Kang L. Extracellular matrix remodelling in obesity and metabolic disorders [J]. *Life Metab*, 2023, 2(4): load021.
- [33] Mujkić R, Šnajder Mujkić D, Ilić I, et al. Early childhood fat tissue changes-adipocyte morphometry, collagen deposition, and expression of CD163+ cells in subcutaneous and visceral adipose tissue of male children[J]. *Int J Environ Res Public Health*, 2021, 18(7): 3627.
- [34] Jiang Y, Guo JQ, Wu Y, et al. Excessive or sustained endoplasmic reticulum stress: One of the culprits of adipocyte dysfunction in obesity [J]. *Ther Adv Endocrinol Metab*, 2024, 15: 20420188241282707.
- [35] Su É, Villard C, Manneville JB. Mitochondria: At the crossroads between mechanobiology and cell metabolism [J]. *Biol Cell*, 2023, 115(9): e2300010.
- [36] Hma J, Ne S, Di Z, et al. Exercise inhibits NLRP3 inflammasome activation in obese mice via the anti-inflammatory effect of meteorin-like[J]. *Cells*, 2021, 10(12): 3480.
- [37] Shook BA, Wasko RR, Mano O, et al. Dermal adipocyte lipolysis and myofibroblast conversion are required for efficient skin repair[J]. *Cell Stem Cell*, 2020, 26(6): 880-895. e6.

收稿日期:2025-08-26 修回日期:2025-08-30 本文编辑:王悦