•综述•

类风湿关节炎中糖脂代谢交互机制与干预策略的研究进展

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摘要: 类风湿关节炎 (rheumatoid arthritis, RA) 作为一种慢性自身免疫性疾病, 其病理进程与糖脂代谢存在复杂的相互影响。糖代谢重编程通过破坏微环境代谢稳态, 激活有氧糖酵解驱动滑膜细胞增殖与炎症; 脂代谢紊乱通过脂源性介质重塑炎症调控网络。糖脂代谢交互影响共同驱动“代谢−炎症”恶性循环, 其中乙酰辅酶A的代谢枢纽作用、代谢物乳酸的双向调控、代谢信号的协同调控以及线粒体−脂滴的细胞器互作加重RA病理进程。本文聚焦RA糖代谢、脂代谢两大核心途径的异常特征及其交互机制, 并基于代谢靶点提出靶向代谢稳态的干预策略及研究方向, 为深入解析RA病理机制及开发靶向代谢干预疗法提供重要科学参考。

关键词: 糖脂代谢; 类风湿关节炎; 代谢重编程; 炎症; 代谢干预疗法

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Research progress on the interaction mechanism of glucose and lipid metabolism and intervention strategies in rheumatoid arthritis

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Abstract: Rheumatoid arthritis (RA), a chronic autoimmune disease, has a complex interaction with glucose and lipid metabolism in pathological process. Glucose metabolism reprogramming disrupts the metabolic homeostasis of the microenvironment and activates aerobic glycolysis to drive synovial proliferation and inflammation; lipid metabolism dysfunction reshapes the inflammatory regulatory network through lipid-derived mediators. The interplay between glucose and lipid metabolism jointly drives the "metabolism-inflammation" vicious cycle, in which the metabolic hub role of acetyl coenzyme A, the bidirectional regulatory role of lactate, the synergistic regulation of metabolic signals, and the organelle interaction between mitochondria and lipid droplets collectively exacerbate the pathological progression of RA. This review systematically focuses on the abnormal characteristics and interaction mechanisms of the two core pathways of glucose and lipid metabolism in RA, proposes intervention strategies and research directions targeting metabolic homeostasis based on metabolic targets, and provides important scientific references for the in-depth analysis of the pathological mechanism of RA and the development of targeted metabolic intervention therapies.

Key words: glucose and lipid metabolism; rheumatoid arthritis; metabolism reprogramming; inflammation; metabolic intervention therapy

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类风湿关节炎 (rheumatoid arthritis, RA) 是一种以关节滑膜慢性炎症为特征的自身免疫性疾病, 其发病机制涉及免疫系统失调、滑膜增生和关节炎症, 最终导致骨侵蚀和关节畸形[1]。RA 传统病理机制主要聚焦于自身免疫反应与细胞因子风暴。机体免疫系统识别异常信号并激活大量免疫细胞, 释放如肿瘤坏死因子 (tumor necrosis factor, TNF)、白细胞介素 (interleukin, IL)-6 等多种细胞因子, 持续推动恶性炎症的发生发展[2]。近年来, 代谢调控已逐渐成为 RA 研究中的核心内容。一方面, 炎症病灶局部氧分压下降及能量需求激增, 促使免疫细胞通过“Warburg 效应”偏向糖酵解途径; 另一方面, 脂质代谢紊乱可调节免疫细胞的基因表达, 放大炎症因子级联释放。糖脂代谢作为维持细胞能量稳态与功能可塑性的核心调控轴, 其异常重编程不仅为活化相关细胞提供代谢底物, 更通过代谢产物介导信号传导重塑炎症微环境。代谢−炎症相互关联, 糖脂代谢异常改变驱动滑膜炎、骨破坏等病理损伤; 免疫稳态失调直接诱导全身炎症, 不断形成恶性循环[3]。本文主要阐明糖脂代谢重编程对 RA 病理进程的影响及其交互机制, 并梳理靶向糖脂代谢关键分子的药物, 以期从糖脂代谢重编程视角为揭示 RA 核心机制和靶向治疗策略提供理论依据。

1 糖代谢重编程

1.1 糖代谢与炎症驱动

糖代谢作为细胞能量供应的核心途径, 其重编程在 RA 代谢紊乱中至关重要。糖代谢途径包括葡萄糖有氧氧化、无氧酵解及磷酸戊糖途径 (pentose phosphate pathway, PPP)[4]。生理状态下, 正常细胞通过氧化磷酸化将其转化为 CO_2 和 H_2O, 并产生 ATP。而 RA 滑膜微环境中, 大量炎性细胞恶性增殖是诱发糖代谢重编程的重要因素之一, 即便氧分压正常, 异常活化的滑膜细胞与免疫细胞仍优先采用糖酵解供能, 即“Warburg 效应”[5]。PPP 作为糖代谢的分支通路, 在生理条件下通过生成还原性辅酶 II (nicotinamide adenine dinucleotide phosphate, NADPH) 维持胞内氧化还原稳态。但 RA 炎症微环境中升高的炎性细胞因子通过干扰 PPP 限速酶葡萄糖-6-磷酸脱氢酶的活性并降低其代谢通量, 使得 PPP 生成 NADPH 的能力受限, 削弱细胞抗氧化能力的同时加剧氧化应激损伤。

1.2 糖代谢信号与调控机制

1.2.1 成纤维滑膜细胞 从氧化磷酸化转变为糖酵解介导的 ATP 产生是成纤维滑膜细胞 (fibroblast-like synoviocytes, FLS) 的代谢特征, 这一过程与 RA 滑膜微环境中炎症因子及缺氧信号密切相关[6]。FLS 的“Warburg 效应”不仅表现为糖酵解途径的显著增强, 更通过信号整合驱动病理进程。已有研究证实, JAK/STAT 通路介导了 RA 发病机制中 FLS 糖代谢重编程与炎症之间复杂的交互作用, 该机制可能是通过核因子 κB (nuclear factor kappa-B, NF-κB)、缺氧诱导因子 (hypoxia inducible factor, HIF)-1α 和磷脂酰肌醇 3-激酶的双向信号耦合实现的[7]。转录因子 NF-κB 作为炎症反应核心调控枢纽, 其磷酸化会上调 HIF-1α 的表达, 进而增加葡萄糖转运体和糖酵解酶基因的表达, 显著提高 FLS 有氧糖酵解活性, 满足 FLS 在炎症微环境中高度活跃的增殖与功能需求[8,9]。同时, 高度糖酵解的 FLS 表现出更强的迁移和侵袭能力, 浸润至周围的关节软骨和骨组织, 从而导致骨破坏的发生。这种侵袭性表型的形成归因于糖酵解途径产生的能量和物质支持了细胞骨架的重塑以及己糖胺通路的激活促使炎症因子的合成与分泌[10]。此外, 己糖胺通路的中间产物尿苷二磷酸 *N*-乙酰葡糖胺可通过 *O*-GlcNAc 糖基化修饰调控转录因子的 DNA 结合能力, 进而促进基质金属蛋白酶 (matrix metalloproteinase, MMP)-3 和 IL-6 等促炎因子基因的转录和表达[11], 这为 RA 滑膜侵袭性生长提供持续的代谢与炎症驱动力。

1.2.2 免疫细胞 RA 免疫细胞的糖酵解活化通过多重机制推动病理进程。$CD8^+$ T 细胞中糖酵解途径相关代谢酶呈现高表达状态, 包括葡萄糖转运蛋白 1 (glucose transporter 1, GLUT1)、己糖激酶 2 (hexokinase 2, HK2), 同时释放促炎介质和细胞毒性介质, 加深炎症反应和关节破坏[12]。而 $CD4^+$ T 细胞更倾向于将葡萄糖分流到 PPP 途径, 增加 NADPH 的生成并消耗活性氧 (reactive oxygen species, ROS), 受损的氧化信号激活下游的白细胞和间质细胞, 从而加剧 RA 的炎症反应。

辅助性 T 细胞 17 (T helper 17, Th17)/调节性 T 细胞 (regulatory T, Treg) 平衡轴利用能量代谢差异塑造细胞功能表型。糖酵解产生的能量和代谢产物能够满足 Th17 细胞快速增殖及合成和分泌大量促炎细胞因子的需求。相反, Treg 细胞则主要依赖于氧化磷酸化供能并借助于其表面高表达的叉头状转录因子 3 (forkhead box protein 3, Foxp3) 发挥免疫抑制功能[13]。RA 滑膜微环境中, 炎症细胞因子如 TNF-α、干扰素 (interferon, IFN)-γ 对 Foxp3 表达的干扰可能是 Th17/Treg 轴失衡引发免疫异常的原因之一。TNF-α 与 TNFR1 结合启动 NF-κB 信号级联, 抑制 Foxp3 基因的转录, 降低 Foxp3 蛋白表达水平[14]; IFN-γ 激活的 JAK-STAT1 通路干扰 Foxp3 蛋白的翻译后修饰稳定性, 使其更易被泛素−蛋白酶体系统降解。TNF-α 与 IFN-γ 借助转录抑制与翻译后修饰双重机制干扰 Foxp3 表达,

诱导Th17/Treg免疫平衡轴的系统性紊乱。值得注意的是, 炎症微环境中的氧化应激致使Treg细胞线粒体膜电位受损, 抑制其线粒体氧化磷酸化能力, 进一步削弱免疫抑制功能[15]。上述机制共同作用致使Treg细胞对Th17细胞的抑制效能显著下降, 形成促炎代谢驱动免疫失衡的正反馈循环。

巨噬细胞代谢表型与其功能极化密切相关, 促炎M1型巨噬细胞选择糖酵解以满足免疫激活初期对物质合成的需求, 而抗炎M2型巨噬细胞则依赖于氧化磷酸化提供必需的代谢底物以维持抗炎功能和组织修复[16]。RA微环境中过量促炎因子如TNF-α、IL-1β和IL-6通过激活MAPK通路 (细胞外信号调节激酶1/2、c-Jun氨基末端激酶和P38激酶) 驱动巨噬细胞向M1型极化, 引发糖酵解相关基因过表达及炎症因子的过量释放, 这一过程通过代谢信号通路调控实现[17]。异常活化的糖酵解为巨噬细胞极化供能并引发一系列级联反应。促炎脂质代谢物前列腺素E2 (prostaglandin E2, PGE2) 结合G蛋白偶联受体激活异源三聚体G蛋白介导的信号通路, 间接维持MAPK通路的持续磷酸化状态[18], 上调M1巨噬细胞相关炎症基因表达。有研究表明, PGE2在佐剂性关节炎 (adjuvant arthritis, AA) 大鼠巨噬细胞中表达增加, PGE2的持续刺激导致EP4过度脱敏, 增强糖酵解关键酶活性, 为M1极化提供代谢支持[19]。在完全弗氏佐剂诱导的关节炎小鼠模型中, 抑制MAPK通路可下调IL-1β、IL-6等促炎因子表达, 显著降低糖酵解水平, 展现出抗RA活性[20]。由此, 靶向免疫代谢检查点与免疫代谢交互通路的双重干预策略, 有望为RA精准治疗提供新突破。

1.2.3　糖源代谢产物　越来越多的研究关注代谢产物作为信号分子在RA中的调控作用。抗炎代谢物衣康酸由顺乌头酸在顺乌头酸脱羧酶催化下经脱羧反应生成, 作为巨噬细胞内三羧酸 (tricarboxylic acid, TCA) 循环特异性代谢物, 通过双重机制抑制炎症级联反应: ① 炎症小体抑制效应: 衣康酸通过抑制TCA循环中琥珀酸脱氢酶活性, 下调琥珀酸表达水平从而抑制ROS过量生成, 阻断炎症小体激活[21]。② 抗氧化信号激活: 衣康酸通过共价修饰KEAP1蛋白中半胱氨酸残基, 激活Nrf2介导的抗氧化信号, 减轻氧化应激损伤, 间接抑制炎症反应[22]。在II型胶原诱导的关节炎大鼠模型中, 关节内注射衣康酸可通过抑制FLS线粒体氧化磷酸化和糖酵解代谢活性, 显著减轻骨质侵蚀和炎症反应[23,24]。2024年《Nature》首次揭示内源性衣康酸对糖皮质激素在RA患者体内的抗炎作用至关重要, 提示衣康酸具有RA生物标志物潜力和治疗价值[25]。糖酵解升高导致乳酸大量释放堆积可能是炎性微环境酸化的原因, 乳酸持续性蓄积促进RA慢性炎症[26]。乳酸不仅是糖酵解终产物, 还可通过激活G蛋白偶联受体促进FLS侵袭, 经组蛋白乳酸化修饰维持巨噬细胞促炎表型。在RA滑膜微环境中, 积累的乳酸重塑$CD4^+$ T细胞的效应表型, 进而增加炎症因子的分泌。糖代谢重编程与RA病理形成双向调控网络, 炎症因子持续激活糖酵解, 而代谢产物又通过表观遗传修饰或受体信号重塑免疫微环境, 最终导致关节发生不可逆性破坏。因此, 靶向衣康酸、乳酸等关键代谢产物, 通过抑制促炎代谢信号与增强抗炎代谢机制的双重调控, 有望推动RA治疗从单纯抗炎向“代谢–炎症”稳态重塑的精准模式转变。

2　脂代谢重编程

2.1　脂代谢与病理关联

脂质代谢通过脂肪酸、胆固醇及磷脂的动态平衡调控, 在能量供应、膜结构构建及炎症信号传导中发挥核心作用。RA滑膜微环境中炎症信号触发滑膜细胞代谢异常[27]: 一方面增强糖酵解代谢流, 为脂质合成提供必需前体; 另一方面通过分子调控网络促进脂肪酸合成酶的生成, 导致细胞内脂质过度沉积。脂代谢紊乱诱发高密度脂蛋白 (high density lipoprotein, HDL) 构象改变, 降低胆固醇逆向转运效率。同时HDL抗氧化抗炎功能衰减, 加剧脂质过氧化与炎症级联放大效应[28]。伴随氧化应激环境恶化, 低密度脂蛋白发生病理性修饰形成致炎物质, 加剧免疫细胞向血管壁的异常迁移与浸润, 最终形成血管炎症的恶性循环[29]。这种脂代谢–炎症网络交互作用为RA的慢性进展提供了关键病理基础。

2.2　脂代谢信号与调控机制

2.2.1　成纤维滑膜细胞　在RA进展中, 成纤维滑膜细胞的脂代谢重构不仅是能量供应的适应性改变, 更是促炎表型获得的关键驱动力。脂肪因子通过双重信号轴调控FLS的炎症与侵袭表型[30]。脂联素通过激活AMPK信号通路抑制FLS内NF-κB核转位, 显著下调TNF-α、IL-6及MMP-1/MMP-3的表达水平, 进而抑制滑膜炎症及细胞外基质降解[31]。与脂联素相反, 瘦素被认为是一种促炎脂肪因子[32]。瘦素通过JAK/STAT通路诱导FLS分泌促炎因子及MMP-13, 加剧细胞外基质降解进程。研究发现, 瘦素受体拮抗剂可特异性逆转FLS的促炎表型, 改善实验性关节炎的软骨损伤, 提示靶向FLS脂代谢通路的治疗价值[33]。深入分析脂质代谢物的生物学效应发现, 不同代谢产物在RA中呈现显著的病理异质性。游离脂肪酸 (free fatty acid, FFA) 通过TLR4/NF-κB信号轴剂量依赖性诱导IL-8

和MMP-3表达, 增强FLS侵袭性。另一促炎脂质介质白三烯B4 (leukotriene B4, LTB4) 通过结合其受体, 诱导TNF-α/IL-1β自分泌并增强MMP-3表达, 协同促进滑膜细胞的增殖和侵袭[34]。促炎脂质代谢物如花生四烯酸代谢物15(*S*)-羟化二十碳四烯酸可通过上调FLS中MMP-2表达, 导致关节软骨侵蚀和骨组织的破坏。相反, 多不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 如二十碳五烯酸可竞争性抑制COX-2活性, 减少PGE2生成, 从而抑制FLS的促血管生成能力[35]。这些发现提示, 靶向FLS脂代谢通路可能通过打破“代谢−炎症”恶性循环实现疾病缓解。脂联素与瘦素的功能拮抗特征及脂质代谢物的异质性, 为开发靶向“代谢−炎症”交互调控的治疗策略提供了理论依据, 特别是在选择性调节脂肪因子信号传导方向展现出临床转化潜力。

2.2.2 免疫细胞 RA中免疫细胞的脂代谢特征直接决定炎症表型极化与自身免疫反应强度。巨噬细胞作为RA关节微环境中的核心免疫调节者, 其极化状态与脂代谢信号紧密关联。M1/M2巨噬细胞表型转换由脂肪因子精密调控, 瘦素通过JAK2/STAT3通路促进M1型极化及IL-1β分泌, 而脂联素通过AMPK诱导M2型转化并增强Treg细胞的免疫抑制功能[36]。T细胞亚群平衡亦受脂质信号影响。RA微环境中持续的炎症刺激致使T细胞磷脂代谢稳态失调, 特异性调控PI3K-Akt信号通路的磷酸化修饰, 通过下游信号级联反应激活哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR)。这种代谢重编程现象不仅促进Th1/Th17细胞分化及其炎症因子分泌, 还通过抑制Foxp3转录因子的表达稳定性削弱Treg细胞功能, 最终打破T细胞亚群平衡并驱动炎症级联反应[37]。研究表明, 炎症小鼠模型中PI3K-Akt通路关键位点磷酸化上调驱使Treg细胞表达受阻, Th1/Th17细胞比例增加, 促进IFN-γ、IL-17的分泌, 加重炎症[38]。树突状细胞 (dendritic cell, DC) 作为连接固有免疫与适应性免疫的桥梁, 其代谢平衡受脂质信号的动态调控。过量炎症因子通过激活DC表面的Toll样受体, 促使鞘氨醇激酶信号通路活化, 上调鞘氨醇-1-磷酸 (sphingosine-1-phosphate, S1P) 的表达, S1P通过与G蛋白偶联受体结合激活下游信号通路, 驱动DC极化迁移并诱导炎症趋化因子释放, 加剧RA炎症级联反应及自身免疫病理进程[39]。中性粒细胞作为炎症早期的关键效应细胞, 其脂代谢特征对疾病进展具有重要影响。RA脂代谢重编程诱导ROS过量生成, 通过蛋白精氨酸脱亚胺酶4依赖性途径催化组蛋白瓜氨酸化, 促使中性粒细胞胞外陷阱持续形成。此过程不仅直接损伤关节滑膜细胞及细胞外基质, 还可激活自身免疫应答, 进一步加重RA关节炎症和组织损伤[40]。由此, 靶向脂代谢信号通路与免疫细胞功能调控节点的联合干预方案, 有望为RA的有效治疗开辟新路径。

2.2.3 脂源性介质 脂源性介质的动态平衡破坏是RA“代谢−炎症”恶性循环的核心驱动力。促炎脂质介质 (LTB4、PGE2、15-HETE等) 通过诱导滑膜细胞增殖、炎性细胞浸润及血管新生, 同时抑制组织修复信号, 驱动RA病理进展; 而抗炎/促消退介质 (保护素、解聚素、脂氧素等) 则通过拮抗炎症信号, 削弱炎症反应, 重建代谢−免疫稳态。这种双向调控特性使得脂质代谢网络既是病理放大器, 也是潜在生物标志物和干预靶标。近年研究揭示, 脂质代谢酶的异常表达是RA脂源性介质失衡的关键机制。如5-脂氧合酶 (5-lipoxygenase, 5-LOX) 活性上调导致LTB4过度生成[41], 而环氧化酶-2 (cyclooxygenase-2, COX-2) 介导的PGE2合成增加与滑膜血管翳形成直接相关[42]。针对这些代谢酶的抑制剂 (5-LOX抑制剂齐留通、COX-2选择性抑制剂塞来昔布) 已在临床前模型中显示出抑制滑膜增生和骨侵蚀的疗效。氧化磷脂作为脂质过氧化代谢产物, 通过双重机制调控免疫反应[43]。一方面, 其作为炎症信号分子激活膜表面Toll样受体启动信号级联, 调控炎症相关基因的表达, 诱导IL-1β、TNF-α、IL-6等促炎细胞因子分泌, 放大关节局部炎症反应; 另一方面, 氧化磷脂的脂毒性可直接损伤关节软骨细胞和滑膜细胞, 抑制软骨基质中蛋白聚糖、胶原蛋白合成, 上调MMP的表达和活性, 致使关节软骨破坏与骨侵蚀, 引发关节畸形。当前研究前沿聚焦于脂质信号受体的精准调控, 如LTB4受体拮抗剂和PUFA激动剂等已进入临床前研究阶段, 而激活抗炎介质受体及内源性介质 (保护素) 可促进炎症消退和组织修复。这些进展标志着RA治疗从单一抗炎模式向“代谢−免疫”多轴调控的转变, 为突破难治性RA提供了新思路。

3 糖脂代谢交互调控网络

3.1 乙酰辅酶A

糖代谢与脂代谢通过代谢枢纽乙酰辅酶A在物质代谢层面和基因调控方面交织互作, 协同驱动RA病理状态下的代谢重编程。生理状态下, 葡萄糖循糖酵解途径转变为丙酮酸, 后者在线粒体中由丙酮酸脱氢酶复合体催化为乙酰辅酶A, 进而进入TCA循环彻底氧化分解供能。RA炎性微环境下, TNF-α、IL-6等炎性因子引发线粒体功能紊乱, 丙酮酸脱氢酶激酶活性上调, 致使丙酮酸脱氢酶复合体磷酸化失活, 丙酮酸无法完全转化为乙酰辅酶A参与TCA循环, 转而通过乳酸

脱氢酶生成乳酸排出细胞, 形成有氧糖酵解表型[44]。代谢流改变致使部分乙酰辅酶A从线粒体溢出至胞浆, 在乙酰辅酶A羧化酶催化下转化为丙二酰辅酶A, 加剧脂肪酸合成通路亢进, 打破脂质代谢平衡[45]。此外, 乙酰辅酶A在表观遗传层面也可参与糖脂代谢的转录调控。RA滑膜组织中蓄积的乙酰辅酶A激活组蛋白乙酰转移酶活性, 特异性调控Foxp3基因启动子与CNS2区域H3K27的乙酰化修饰, 上调Foxp3表达, 维持Treg细胞的免疫抑制功能, 抑制炎症级联效应[46]。代谢枢纽乙酰辅酶A不仅在物质代谢层面通过“糖酵解-TCA循环-脂质合成”路径实现糖脂互联, 更通过表观遗传机制直接调控炎症反应, 为靶向关键代谢酶通路以干预RA代谢重编程提供了新方向。

3.2　乳酸

传统研究将乳酸视为糖酵解的终末产物或能量代谢的过渡载体, 其在病理过程中的作用常被简化为缺氧微环境的被动标志物。然而, 新近证据揭示乳酸在RA中的双重角色, 既能通过代谢干预短暂缓解炎症损伤, 又能在特定病理条件下转变为推动疾病恶化的主动调控因子。在RA早期或局部急性炎症阶段, 乳酸可通过G蛋白偶联受体81抑制脂解, 减少促炎性FFA的释放[47]; 同时增强线粒体氧化代谢以维持细胞稳态, 发挥短暂的保护性效应。随着病程进展和炎症持续, 微环境中乳酸浓度突破生理阈值, 过量的乳酸通过激活HIF-1α信号通路维持糖酵解亢进, 形成代谢恶性循环; 此外, 高水平乳酸经单羧酸转运蛋白转运至线粒体氧化为丙酮酸, 后者既进入TCA循环参与能量代谢, 也可作为底物在脂质氧化过程补充草酰乙酸, 间接促进脂质氧化[48], 加速氧化应激和脂毒性损伤。值得关注的是, 慢性高乳酸状态可能是引发免疫细胞功能紊乱的重要诱因, 如解除对炎症因子分泌的抑制并促进自身反应性T细胞分化, 推动关节破坏进程。这种双重角色的动态转化与乳酸浓度梯度、作用时间及靶细胞类型密切相关, 反映了糖脂代谢在应对持续炎症压力时从代偿到失代偿的转变过程。因此, 针对乳酸的治疗策略需精准区分其保护性与致病性作用阶段, 以实现对RA病理的针对性干预。

3.3　线粒体–脂滴

脂滴最初被视作静态脂肪储存细胞器, 其形成实则是细胞应激反应的重要标志[49]。RA滑膜细胞中异常亢进的有氧糖酵解导致线粒体氧化磷酸化功能受损, 引发ROS的异常累积。此时细胞通过诱导脂滴形成, 将脂肪酸隔离于脂滴核心, 以减少脂肪酸对线粒体的直接毒性作用, 有效抵御应激损伤[50]。然而随着病程进展, 长期糖代谢紊乱可进一步引发线粒体FFA氧化功能缺陷, 表现为代谢酶的表达水平及活性下调, 致使脂滴内储存的脂肪酸无法有效进入线粒体参与氧化分解。当线粒体–脂滴间的细胞器互作被破坏, 脂肪酸隔离功能丧失, 引发脂毒性代谢物外溢, 即未被及时清除的脂肪酸通过诱导内质网应激和线粒体膜通透性改变, 驱动炎症因子释放与细胞焦亡, 最终形成糖脂代谢异常和细胞器互作紊乱的恶性循环[51,52]。针对线粒体–脂滴互作中的脂肪酸转运酶 (肉碱/有机阳离子转运体2), 可能打破RA代谢恶性循环, 为疾病修饰治疗提供新的潜在靶点。

3.4　HIF-1α/PPARγ信号

滑膜内膜增生和免疫细胞浸润形成缺氧微环境, HIF是RA滑膜组织中对缺氧环境响应的关键调节因子。越来越多的证据支持缺氧和HIF调节RA的重要病理生理特征, 包括滑膜炎症、血管生成和软骨破坏[53]。HIF-1α与过氧化物酶体增殖物激活受体γ (peroxisome proliferator activated receptor γ, PPARγ) 协同调控糖脂代谢的交互失衡, 加重病理进程。HIF-1α的持续激活不仅通过与靶基因启动子区域的缺氧反应元件结合, 上调GLUT1、HK2等糖酵解关键酶的表达水平以增强糖酵解过程, 为细胞在缺氧条件下提供快速ATP供给。同时, HIF-1α通过表观遗传抑制, 显著削弱PPARγ的脂代谢调控功能[54]。而HIF-1α/PPARγ的协同调控直接导致糖代谢亢进和脂代谢抑制的失衡状态, 即糖酵解产生的柠檬酸无法通过PPARγ依赖的线粒体–脂滴互作进入TCA循环, 反而通过ATP柠檬酸裂解酶转化为乙酰辅酶A, 进一步促进脂质合成和脂滴堆积, 加剧脂质代谢紊乱。

研究表明, PPARγ激动剂罗格列酮可逆转HIF-1α驱动的代谢失衡: 一方面通过激活PPARγ的转录活性, 上调脂肪酸转运蛋白、脂肪酸结合蛋白及肉碱棕榈酰转移酶1等脂质代谢关键基因的表达, 显著促进脂肪酸的摄取及氧化分解过程[55]; 另一方面, PPARγ激活还可通过抑制糖酵解亢进驱动的炎症信号通路, 减少炎症因子的表达与释放, 从而改善RA滑膜细胞的炎症微环境[56]。HIF-1α/PPARγ的协同调控提供了潜在干预靶点 (PPARγ激动剂或HIF-1α降解诱导剂)。这种干预策略揭示HIF-1α/PPARγ的协同调控不仅是糖脂代谢的调控机制, 更是连接代谢异常与炎症的分子桥梁。

4　结语与展望

糖脂代谢重编程参与RA的发生发展, 在炎性微环境下细胞优先选择有氧糖酵解并同步激活脂质合成与代谢重塑, 维持细胞异常增殖及炎症放大, 形成“代谢–炎症”反馈路径, 加速RA进展 (图1、2)。其中,

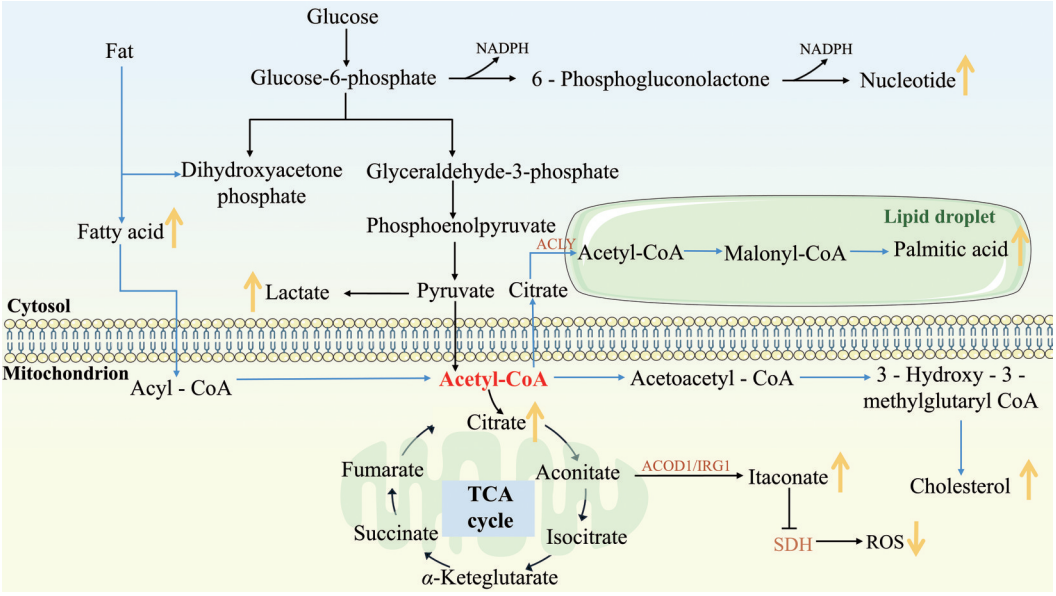


Figure 1 The interplay and regulatory mechanisms between intracellular glucose and lipid metabolism. After entering the cell, glucose is converted to glucose-6-phosphate, which can either enter the PPP to generate nucleotides or undergo glycolysis to produce pyruvate. Pyruvate enters the mitochondria and is converted into acetyl-CoA to participate in the TCA cycle. Citrate from the TCA cycle is transported to the cytosol for fatty acid synthesis and stored in lipid droplets. Fatty acids also enter the mitochondria *via* acyl-CoA for metabolism. The black lines represent glucose metabolism, and the blue lines represent lipid metabolism. PPP: Pentose phosphate pathway; TCA: Tricarboxylic acid; NADPH: Nicotinamide adenine dinucleotide phosphate; ACLY: ATP-citrate lyase; ACOD1: Aconitate decarboxylase 1; IRG1: Immune-responsive gene 1; SDH: Succinate dehydrogenase; ROS: Reactive oxygen species; CoA: Coenzyme A

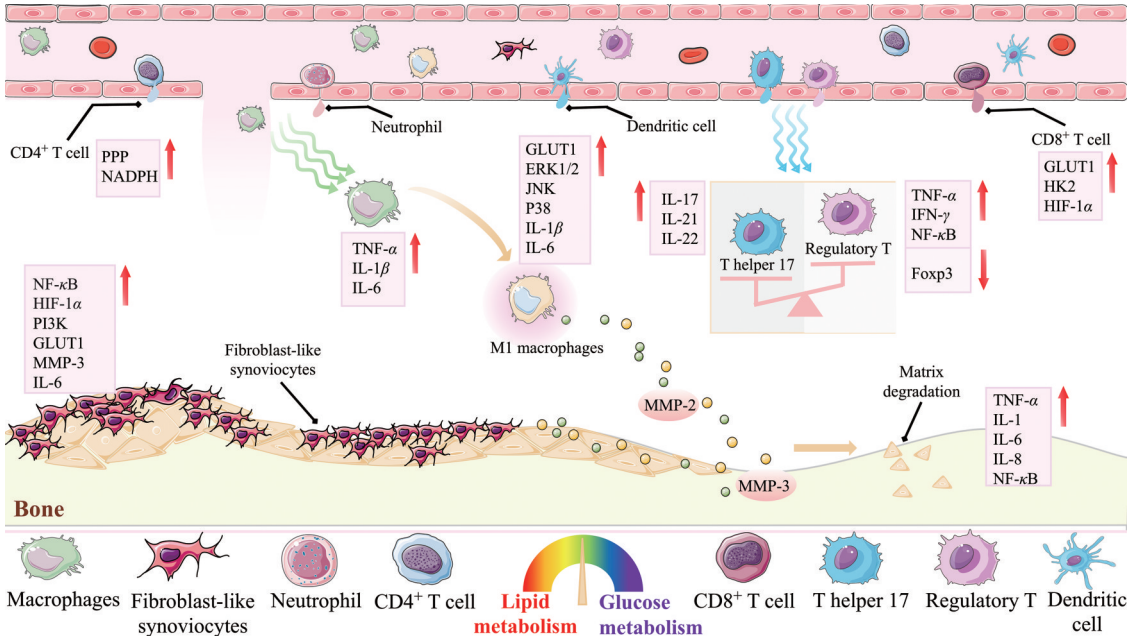


Figure 2 Complex interactions and metabolic regulatory mechanisms among immune cells and joint tissue cells in RA. Abnormal glucose and lipid metabolism drives macrophage polarization toward the pro-inflammatory M1 phenotype, disrupting the regulatory T/T helper 17 balance axis. Fibroblast-like synoviocytes are activated by cytokines. These activated FLS and macrophages collectively secrete MMPs. $CD4^+$ T cells produce NADPH through the PPP, and $CD8^+$ T cells upregulate molecules such as GLUT1. RA: Rheumatoid arthritis; GLUT1: Glucose transporter 1; NF-κB: Nuclear factor kappa-B; HIF-1α: Hypoxia inducible factor-1α; PI3K: Phosphatidylinositol 3-kinase; MMP-3: Matrix metalloproteinase-3; IL: Interleukin; TNF-α: Tumor necrosis factor-α; ERK1/2: Extracellular signal-regulated kinase 1/2; JNK: Cellular Jun protein (c-Jun) N-terminal kinase; P38: P38 mitogen-activated protein kinase; IFN-γ: Interferon-γ; Foxp3: Forkhead box protein 3; HK2: Hexokinase 2

PPARγ、MAPK等信号兼具代谢调控和免疫应答功能，靶向上述关键代谢过程和相关信号通路成为解析RA复杂病理机制的关键突破口 (图3)。近年来，靶向这些关键节点的治疗策略已初见成效 (表1[57-72])。甲氨蝶呤作为治疗RA的一线药物[73]，通过抑制二氢叶酸合成酶调控MAPK活性，打破代谢与炎症的耦合效应，

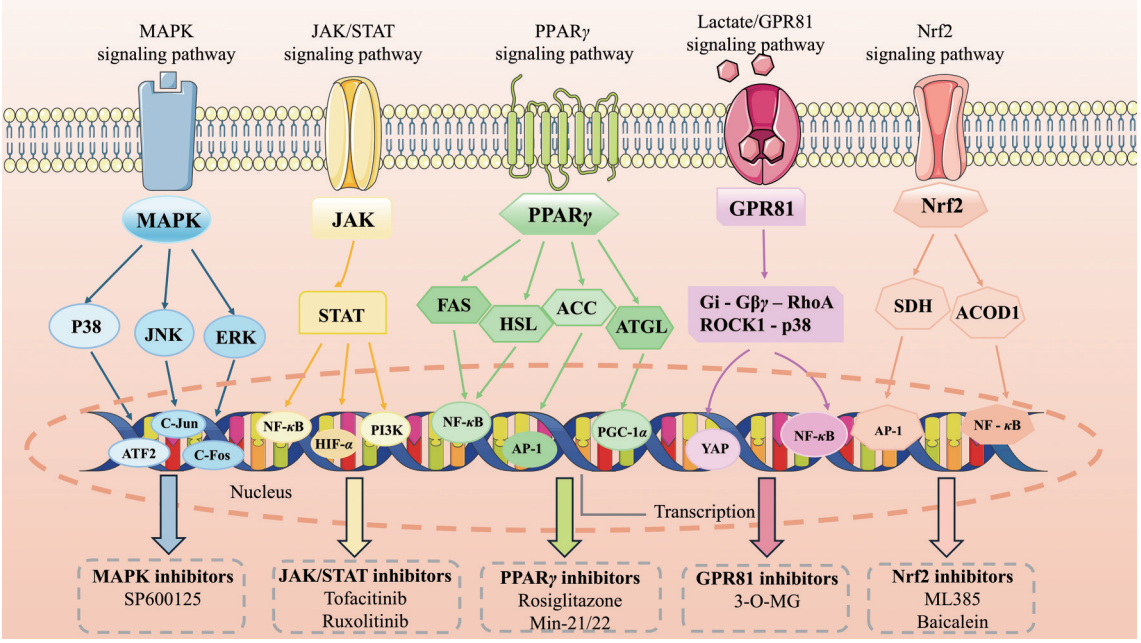


Figure 3　Main signaling pathways and inhibitors related to RA. The MAPK signaling pathway, JAK/STAT signaling pathway, PPARγ signaling pathway, lactate/GPR81 signaling pathway, and Nrf2 signaling pathway are the main signaling pathways involved in the process of RA. MAPK: Mitogen-activated protein kinase; ATF2: Activating transcription factor 2; c-Fos: Cellular fos protein; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; PPARγ: Peroxisome proliferator activated receptor γ; FAS: Fas protein; HSL: Hormone-sensitive lipase; ACC: Acetyl coenzyme A carboxylase; ATGL: Adipose triglyceride lipase; AP-1: Activator protein 1; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1α; GPR81: G protein-coupled receptor 81; YAP: Yes-associated protein; Nrf2: Nuclear factor erythroid 2-related factor 2

Table 1　Intervention strategies targeting glucose and lipid metabolism in RA. DHFR: Dihydrofolate reductase; AMPK: AMP-activated protein kinase; SIRT1: Silent information regulator 1; NLRP3: NOD-like receptor pyrin domain-containing protein 3; HDAC6: Histone deacetylase 6; MCC950: CRID3 sodium salt; M808: Hydroxamic acid; BrPA: 3-Bromopyruvic acid

Drug/ Compound	Target	Mouse (M) or human (H) data	Pharmacological effect	Reference
Methotrexate	DHFR	M, H (phase IV)	T cell proliferation is inhibited and the release of pro-inflammatory cytokines is reduced	[57]
Tofacitinib, ruxolitinib	JAK	M, H (phase IV)	The JAK1/JAK3 pathway is inhibited, blocking cytokine signaling	[58,59]
Eupalinolide B, shikonin	AMPK	M	These drugs can regulate the AMPK signaling pathway and inhibit RA by inducing apoptosis and autophagy	[60,61]
Resveratrol	SIRT1	M, H (phase II)	The expression of inflammatory cytokines is inhibited, and glucose and lipid metabolism as well as mitochondrial function are regulated. It alleviates oxidative stress-induced damage	[62,63]
MCC950	NLRP3	M, H (phase II)	Lipotoxic signals are inhibited, blocking the production of IL-1β	[64,65]
M808	HDAC6	M	It reduces the release of MMPs and cytokines from RA-FLS	[66]
Baicalein, ML385	Nrf2	M	It can inhibit the release of inflammatory mediators and the proliferation of synovial cells	[67]
PF-06650833	IRAK4	M, H (phase II)	Inhibition of IRAK4 reduces cytokine and MMP release in human RA-FLS. *In vivo* administration of PF-06650833 alleviates the severity of collagen-induced arthritis	[68]
3-*O*-MG	GPR81	M	It can inhibit the release of inflammatory cytokines	[69]
SP600125	JNK	M	SP600125 can alleviate joint swelling and bone destruction in mice with collagen-induced arthritis	[70]
Rosiglitazone	PPARγ	M, H (phase II)	It regulates lipid metabolism and inhibits inflammatory pathways	[71]
BrPA	HK2	M	BrPA alleviates RA by inhibiting cell proliferation and promoting cell apoptosis	[72]

减轻炎症反应; JAK抑制剂托法替尼抑制糖酵解限速酶, 下调炎症因子的表达[74,75]; 白藜芦醇显著增强抗氧化酶活性, 有效缓解氧化应激介导的组织损伤, 负反馈调控促炎通路的过度活化; M808作为一种新型HDAC6抑制剂, 可选择性下调微管蛋白乙酰化水平, 阻断滑膜细胞侵袭与炎症信号的级联放大, 减轻滑膜炎症及骨破坏进程; SP600125抗RA作用常依赖于糖脂代谢平衡关键靶点c-Jun氨基末端激酶, 阻断促炎信号传导和炎症因子的过度分泌; NLRP3炎症小体抑制剂MCC950通过遏制脂毒性信号, 展现出滑膜组织代谢重塑的调控潜力, 是目前发现的靶向RA新兴药物之一[76]。然而, 现有代谢干预手段仍存在局限性, 如糖酵解抑制剂可能干扰正常组织能量稳态, 提示需开发选择性的代谢调控药物[77]。

未来研究可聚焦三大方向以应对这一瓶颈研究: ① 解析不同时期的代谢重编程特征, 深入探究早期RA滑膜组织诱导糖脂代谢的分子机制及晚期全身代谢紊乱的级联反应, 明确局部炎症微环境与全身代谢网络的交互调控机制; ② 代谢生物标志物开发, 整合代谢组学及单细胞测序技术, 鉴定滑膜液及血液中特异性代谢物, 构建基于代谢特征的疾病预测模型, 推动RA个性化治疗; ③ 基于代谢分型的RA亚群分类, 如高糖酵解型、脂代谢失调型等特异性代谢表型, 为开发多靶点、亚型特异性治疗方案提供关键线索。综上所述, 糖脂代谢交互机制在RA中的发展进程与靶点干预是生物医学研究的重要方向, 有望推动RA治疗从单纯抗炎向代谢精准干预发展, 具有重要的临床意义。

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