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Hans汉斯

代谢重编程与表观遗传调控在骨关节炎中的协同作用研究进展

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摘 要

骨关节炎(OA)是一种以关节软骨退变为主要病理特征的常见退行性疾病，严重影响患者的生活质量。近年来，代谢重编程和表观遗传调控在OA软骨退变中的作用机制成为研究热点。软骨细胞在OA进展中经历显著的代谢异常，包括糖酵解增强、线粒体功能障碍及脂质代谢紊乱，这些变化与表观遗传修饰(如DNA甲基化、组蛋白乙酰化和非编码RNA调控)密切相关，共同促进软骨降解和炎症反应。本文系统综述了代谢重编程与表观遗传调控在OA软骨退变中的协同作用，阐明二者如何通过交互作用影响软骨细胞稳态，并探讨了靶向代谢–表观遗传通路的潜在治疗策略，为OA的精准干预提供新视角。

关键词

骨关节炎，软骨退变，代谢重编程，表观遗传，协同作用

Research Advances in the Synergistic Effects of Metabolic Reprogramming and Epigenetic Regulation in Osteoarthritis

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Abstract

Osteoarthritis (OA) is a common degenerative disease characterized primarily by cartilage degradation, which severely impairs patients' quality of life. In recent years, the mechanisms of metabolic reprogramming and epigenetic regulation in OA cartilage degradation have become a research hotspot. Chondrocytes undergo significant metabolic abnormalities during OA progression, including enhanced glycolysis, mitochondrial dysfunction, and lipid metabolism disorders. These changes are closely associated with epigenetic modifications (such as DNA methylation, histone acetylation, and non-coding RNA regulation), which together promote cartilage degradation and inflammatory responses. This article systematically reviews the synergistic effects of metabolic reprogramming and epigenetic regulation in OA cartilage degradation, elucidates how they interact to affect chondrocyte homeostasis, and explores potential therapeutic strategies targeting metabolic-epigenetic pathways, providing new insights for the precise intervention of OA.

Keywords

Osteoarthritis (OA), Cartilage Degeneration, Metabolic Reprogramming, Epigenetic, Synergistic Effect

1. 引言

骨关节炎(Osteoarthritis, OA)是全球范围内致残率最高的关节疾病，其核心病理特征是关节软骨的进行性退变，主要表现为软骨细胞功能紊乱和细胞外基质(Extracellular Matrix, ECM)的降解[1]。软骨细胞是软骨唯一常驻细胞，负责 ECM 合成与分解以维持稳态，其功能紊乱直接引发基质降解、软骨破坏，推动 OA 进展[1]。近年研究聚焦代谢重编程(如线粒体障碍、糖酵解增强)与表观遗传调控(DNA 甲基化、组蛋白修饰等)在 OA 中的关键作用：代谢重编程是退变的核心驱动因素，影响软骨细胞存活与功能[2]；表观遗传调控通过可逆的修饰机制在不改变 DNA 序列的情况下精细调控基因表达，参与 OA 进程[3]。二者形成双向互作的“代谢–表观遗传网络”，共同驱动 OA 软骨退变，最终导致软骨细胞衰老、凋亡及 ECM 稳态崩溃[4]。本文将系统阐述这一协同作用的分子机制，并探讨其临床转化价值。

2. 骨关节炎软骨细胞代谢重编程特征

2.1. 糖代谢异常与 Warburg 效应

OA 软骨细胞存在显著代谢重编程，核心特征为有氧条件下优先糖酵解(Warburg 效应) [5]。该效应并非 OA 特有，常见于快速增殖细胞(如癌细胞)，本质是代谢从高效氧化磷酸化转向低效率糖酵解，以满足增殖的能量与生物合成需求[5]。OA 软骨细胞中表现为糖酵解增强、氧化磷酸化受抑[5]；虽线粒体功能未完全受损，但代谢偏好改变使葡萄糖大量转化为乳酸[6]，此表型助力细胞在缺氧/营养匮乏环境中存活[7]。关键机制为糖酵解酶(如限速酶磷酸果糖激酶 PFK)表达上调，PFK 异常与糖代谢紊乱密切相关[8]；斑马鱼 pfkma/pfkmb 双敲除模型显示血糖升高、能量代谢受损，印证 PFK 对糖稳态的核心作用[8]。糖酵解增强致乳酸堆积，酸化关节微环境，促进基质降解酶表达，加速软骨破坏[9]。此外，糖酵解中间产物(如 3-磷酸甘油酸 3-PG、磷酸烯醇式丙酮酸 PEP)既是代谢中间体，又可作为表观遗传酶(组蛋白甲基/乙酰

转移酶)的底物/调节剂，调控软骨细胞基因表达，连接代谢状态与表观遗传[10]。

2.2. 线粒体功能障碍与 ROS 产生

OA 软骨细胞代谢重编程伴随显著线粒体功能障碍，表现为形态异常(肿胀、嵴减少)、ATP 合成效率降低，但活性氧(ROS)生成增加[11] [12]。线粒体 DNA 损伤及电子传递链复合物活性改变加剧氧化应激[13]。过量 ROS (如超氧阴离子、过氧化氢)激活 NF-κB 等信号通路，驱动软骨细胞分泌 IL-1β、TNF-α 等炎症介质，形成恶性循环，加重关节炎症与软骨破坏[14]。同时，ROS 作为信号分子，通过调控氧化还原敏感的表观遗传酶(如 DNA 去甲基化 TET 家族、组蛋白去甲基化 JMJD 家族)，影响 DNA 及组蛋白修饰，重塑软骨细胞表观遗传景观，调控细胞存活、炎症及基质代谢相关基因表达，参与 OA 病理进程[15]。

2.3. 脂质代谢重编程

OA 软骨细胞代谢紊乱还表现为脂质代谢重编程，以脂肪酸合成增强(ACC、FASN 活性上调)和 β-氧化抑制(CPT1 表达下调)为特征[16]。这种转变导致脂质(如甘油三酯)异常堆积，引发脂毒性，诱发内质网应激及软骨细胞凋亡，加速软骨丢失[17]。更关键的是，脂质代谢物(如乙酰辅酶 A、S-腺苷甲硫氨酸 SAM)是代谢与表观遗传的桥梁：乙酰辅酶 A 为组蛋白乙酰化直接底物，调控染色质结构及基因转录；SAM 是 DNA 和组蛋白甲基化反应中关键的甲基供体[18]。综上，脂质代谢重编程既通过脂毒性直接损伤细胞，又通过调控乙酰-CoA、SAM 等代谢物水平，影响表观遗传修饰(组蛋白乙酰化、甲基化等)，调控软骨细胞分化、炎症及基质稳态相关基因表达，是代谢与表观遗传协同的重要环节[18]。

3. 骨关节炎中的表观遗传调控机制

3.1. DNA 甲基化动态变化

研究表明，DNA 甲基化在 OA 软骨退变中起关键调控作用。全基因组甲基化分析显示 OA 软骨存在大量差异甲基化区域，显著富集于 ECM 合成及炎症相关基因[19]。如 COLGALT2 基因启动子区低甲基化可上调其表达，影响胶原糖基化[20]。DNMTs 与 TET 家族蛋白维持甲基化/去甲基化动态平衡，其中 TET 介导的主动去甲基化过程通过调控 SOX9 等软骨形成关键基因影响 OA 进展[21]。代谢重编程与 DNA 甲基化密切相关：α-酮戊二酸(α-KG)、琥珀酸等作为 TET/DNMT 辅助因子，通过影响酶活性调节甲基化平衡[22]；线粒体功能异常致 α-KG/琥珀酸比例改变，可影响关键基因甲基化状态，促进 OA 进展[23]。

3.2. 组蛋白修饰异常

组蛋白修饰异常是 OA 表观遗传调控的重要特征，表现为 OA 软骨细胞中 H3K27me3 整体降低、H3K9ac 增加[24]。这种改变与 EZH2 (催化 H3K27me3 的甲基转移酶)下调、p300/CBP (组蛋白乙酰转移酶)激活相关，二者协同促进促分解代谢基因表达[25]。代谢异常与组蛋白修饰互为调控：SDH/IDH 突变致琥珀酸、2-HG 等堆积，竞争性抑制 JMJD 等组蛋白去甲基化酶活性[22]；乙酰-CoA 作为组蛋白乙酰化直接底物，其水平变化影响乙酰转移酶活性及染色质开放性，OA 中脂肪酸氧化增强致乙酰-CoA 积累，通过促进 H3K9ac 激活 MMP13、ADAMTS7 等基质降解酶的表达[22]。此外，H3K9me2 修饰降低与 ADAMTS-5 表达上调相关，抑制组蛋白去甲基化酶 LSD1 可缓解 OA 小鼠软骨退变[26]。

3.3. 非编码 RNA 调控网络

非编码 RNA (如 miR-140、miR-146a、HOTAIR、MALAT1 等)在 OA 软骨退变中形成复杂调控网络，通过调控 ECM 代谢关键基因参与病理进程[27]。例如，miR-140 靶向抑制 ADAMTS5 以阻止基质降解，其在 OA 中表达下调会加剧降解[28]；环状 RNA (如 ciRS-7)作为 miRNA 海绵参与代谢－炎症正反馈[29]。

代谢应激(如缺氧)可通过 HIF-1α 调控非编码 RNA 表达：缺氧诱导 lncRNA CRNDE，通过招募 p300 促进 H3K27ac 在 DACT1 启动子区富集，抑制 Wnt/β-catenin 通路[30]；ELDR 等 lncRNA 通过形成 hnRNPL/KAT6A 复合物调控 IHH 基因的组蛋白修饰，加速软骨细胞衰老[31]。这些发现揭示非编码 RNA 作为表观遗传调控媒介的核心作用，为 OA 诊断及治疗提供新靶点[32]。

4. 代谢与表观遗传的协同作用机制

4.1. 代谢酶的双重功能

代谢酶在细胞中兼具基础代谢与表观遗传调控双重功能，这一特性在 OA 软骨退变及软骨肉瘤中尤为显著。糖酵解关键酶 PKM2 可在软骨细胞中发生核转位，作为蛋白激酶直接磷酸化组蛋白 H3 第 11 位苏氨酸(H3T11)，激活炎症相关基因表达，且该非经典功能独立于糖酵解活性，通过改变染色质可及性调控转录[33]；其酶活性状态与表观调控功能呈动态平衡——低活性二聚体易通过入核发挥激酶作用，高活性四聚体则驻留胞浆参与糖酵解[34]，而在炎症微环境中 IL-1β 可诱导 PKM2 核转位，通过磷酸化 H3T11 促进 MMP-13、ADAMTS-5 等软骨降解酶的表达[35]。在软骨肉瘤中，异柠檬酸脱氢酶 IDH1/2 突变产生的致癌代谢物 2-羟基戊二酸(2-HG)竞争性抑制 α-KG 依赖性双加氧酶(如 TET/JMJD 家族)，导致全基因组 DNA 高甲基化及组蛋白去甲基化受阻，进而沉默 SOX9 等软骨保护基因并激活促纤维化通路[36]。此外，ATP 柠檬酸裂解酶通过将线粒体柠檬酸转化为核内乙酰-CoA，为组蛋白乙酰转移酶提供底物以连接三羧酸循环与染色质乙酰化[37]，机械应力刺激下其活性升高可促进 H3K27ac 在软骨合成基因启动子区富集，增强 II 型胶原表达[38]。这些机制共同揭示代谢酶通过非经典功能桥接代谢状态与表观遗传调控，驱动关节疾病进展。

4.2. 代谢物作为表观遗传调节剂

细胞内代谢物动态变化通过塑造表观遗传景观形成代谢–表观遗传反馈环路，在 OA 病理中发挥核心作用：SAM 作为通用甲基供体，其水平波动直接影响 DNA 及组蛋白甲基化状态，软骨细胞分化时甲硫氨酸代谢重编程致 SAM/SAH 比率下降，引发 SOX9 启动子区 DNA 低甲基化及增强子区 H3K27me3 去甲基化，从而激活软骨特异性基因表达[39]；NAD+/NADH 比例通过调节 Sirtuin 去乙酰化酶活性调控线粒体功能，NAD+依赖的 SIRT1 去乙酰化 PGC-1α 可促进线粒体生物合成，而 NADH 积累会抑制 SIRT3 活性导致 SOD2 乙酰化增加、抗氧化防御能力下降[40]，OA 中炎症介导的 NAD+耗竭进一步降低 SIRT1 活性，致 NF-κB 通路过度乙酰化及持续炎症反应[41]；α-KG 与琥珀酸的比例作为表观遗传修饰酶的分子开关，通过调控 JmjC 去甲基酶及 TET 蛋白活性决定染色质重塑方向，IDH 突变产生的 2-HG 通过提高琥珀酸/α-KG 比例抑制 TET 介导的 DNA 去甲基化，使 COL2A1 等软骨基质基因启动子区保持高甲基化状态[42]；乙酰-CoA 作为组蛋白乙酰化的直接底物，其浓度与 H3K9ac 水平呈正相关，缺氧条件下丙酮酸脱氢酶激酶抑制 PDH 活性减少乙酰-CoA 生成，导致软骨细胞中促炎基因位点的组蛋白低乙酰化和转录抑制[43]。这些代谢物通过调控甲基化、乙酰化等表观遗传修饰，构成代谢与表观遗传的协同网络，驱动 OA 软骨退变，见表 1。

Table 1. Epigenetic modifications corresponding to key metabolites
表 1. 关键代谢物所对应的表观遗传修饰

代谢物	表观遗传修饰改变	参考文献
SAM/SAH 比率	DNA 甲基化、组蛋白甲基化	[39]
NAD+/NADH 比例	蛋白质去乙酰化(Sirtuin 家族)	[40]
α-KG/琥珀酸比例	DNA 去甲基化(TET 酶)、组蛋白去甲基化(JmjC 酶)	[42]
乙酰-CoA	组蛋白乙酰化	[43]

4.3. 应激信号通路的整合作用

多种应激信号通过代谢–表观遗传网络加剧软骨退变：缺氧通过稳定 HIF-1α 上调糖酵解酶(PKM2, LDHA)，糖酵解增强致 α-KG 减少，进一步稳定 HIF-1α 并抑制 TET 介导的 DNA 去甲基化，形成促分解代谢的正反馈环路[44]；机械应力通过 YAP/TAZ 通路促进 GLUT1 表达(增加葡萄糖摄取)，同时募集 p300 至 RUNX2 启动子区，通过 H3K27ac 修饰促进软骨细胞肥大分化[45]；炎症微环境中 IL-1β 通过 NF-κB 诱导糖酵解酶(HK2, PFKM)表达，同时招募 DNA 甲基转移酶至 miR-140 启动子区，致其高甲基化沉默，削弱对 ADAMTS-5 的抑制[46]；氧化应激消耗 NADPH 改变 GSH/GSSG 比例，影响组蛋白去甲基酶 KDM4A 活性，导致 H3K9me2 异常积累及衰老基因表达[47]。这些应激信号的交叉对话构成 OA 中复杂的代谢–表观遗传调控层级，见图 1。

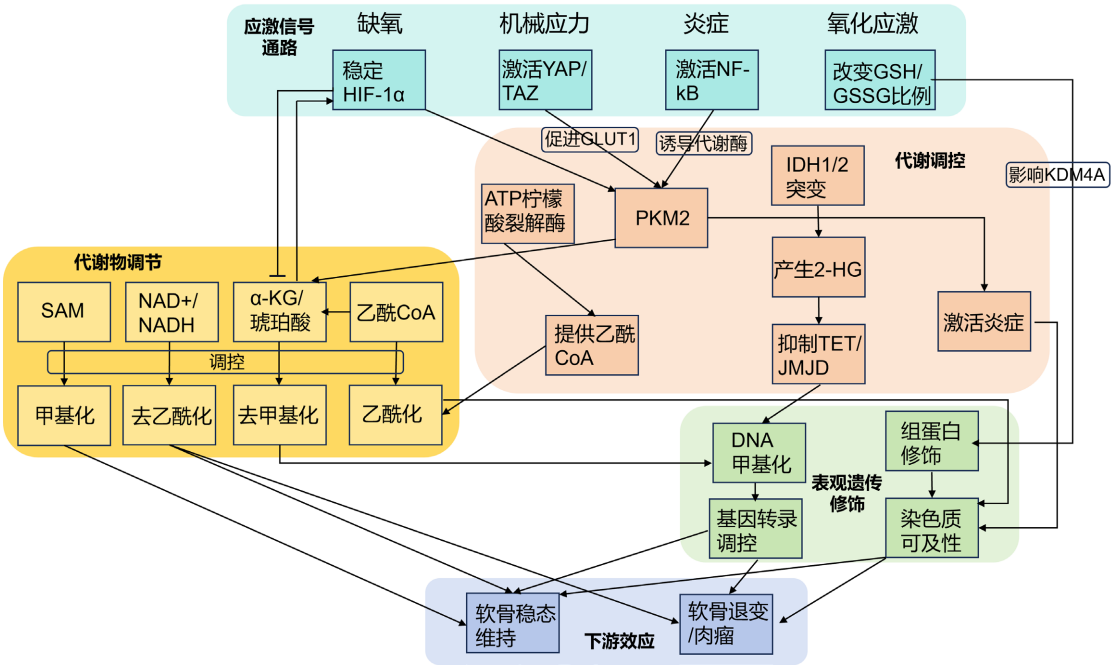

Figure 1. Molecular mechanism diagram of the "metabolic-epigenetic synergy network"
图 1. "代谢–表观遗传协同网络"的分子机制图

5. 靶向代谢–表观遗传网络的干预策略

5.1. 代谢调节剂的应用

靶向代谢通路的调节剂是干预代谢–表观遗传网络的基础策略，通过直接纠正 OA 软骨细胞失调的代谢状态，间接影响依赖代谢物供应的表观遗传酶活性以恢复正常基因表达谱。例如，经典 AMPK 激活剂二甲双胍作用超越单纯降糖，可通过激活 AMPK 并抑制 mTOR 信号通路改善线粒体功能、减少 ROS 产生[48]，更重要的是其激活 AMPK 能调控 SIRT1 等表观遗传调节因子活性，在 OA 模型中通过 AMPK/SIRT1 信号轴发挥抗炎和软骨保护作用，提示可能通过调节 SIRT1 介导的组蛋白去乙酰化等表观遗传修饰起效[49]。直接干预糖酵解是另一途径，糖酵解抑制剂 2-脱氧-D-葡萄糖(2-DG)可限制 OA 软骨细胞异常能量供应，研究显示其在实体瘤中与组蛋白去乙酰化酶抑制剂(HDACi)联合应用可产生协同抗肿瘤效应(HDACi 上调糖酵解，2-DG 抑制 HK2 阻断该通路)，这为 OA 治疗提供新思路——联合糖酵解抑制剂与表观遗传药物或能同时切断异常能量供应与纠正表观遗传失调[50]。最后，鉴于 ROS 积累是诱

导DNA/组蛋白修饰异常的关键因素，抗氧化剂N-乙酰半胱氨酸(NAC)通过补充谷胱甘肽前体清除ROS，可能减少 ROS 介导的异常 DNA 甲基化、组蛋白修饰等表观遗传改变，延缓软骨细胞衰老凋亡，为基础性代谢–表观遗传干预手段[51]。这些策略通过代谢–表观遗传双重调控为 OA 提供综合干预方案。

5.2. 表观遗传药物的开发

直接靶向表观遗传修饰酶是干预代谢–表观遗传网络的另一核心方向，旨在直接逆转 OA 软骨异常基因沉默/激活状态。常见药物包括 DNMT 抑制剂(如 5-氮杂胞苷)、HDAC 抑制剂(如曲古抑菌素 A)，体外实验显示其可恢复软骨细胞表型、上调软骨特异性基因[52]，但临床因缺乏关节靶向性导致全身副作用而受限，需开发关节精准递送系统[53]。CRISPR/dCas9 表观遗传编辑技术通过 dCas9 融合表观效应域(如 TET1、p300)，定点编辑目标基因启动子甲基化/乙酰化状态，精准调控基因表达，为 OA 基因特异性治疗提供工具[54]。此外，miRNA 作为代谢与表观遗传的连接节点，其模拟物/拮抗剂也展现出治疗潜力，如 miR-140 模拟物可补充 OA 软骨中缺失的 miR-140，通过调节下游靶基因发挥软骨保护作用[55]。这些表观遗传药物从不同层面为 OA 代谢–表观遗传网络干预提供多样化精准策略，见图 2。

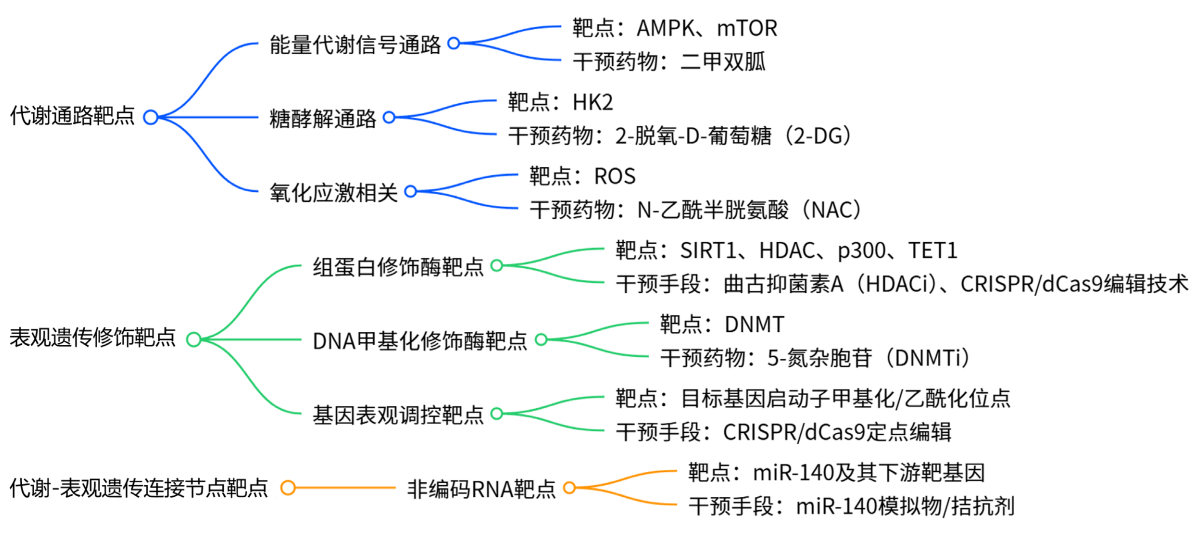

Figure 2. Potential therapeutic targets and intervention strategies
图 2. 潜在治疗靶点及干预策略

5.3. 联合治疗策略的优化

鉴于代谢与表观遗传调控的复杂性及相互依赖性，单一靶点干预效果有限，优化联合治疗策略至关重要。需关注代谢干预与表观遗传调节的时序组合(如先用二甲双胍改善代谢状态，再用 HDAC 抑制剂，协同增效，类似癌症序贯治疗[56])；同时，纳米载体(脂质体、聚合物纳米粒)可设计为关节微环境响应或靶向软骨细胞，提高关节局部药物浓度、减少全身副作用[57]；此外，类器官和关节芯片技术(用患者来源细胞或 iPSCs 构建)能模拟体内关节环境[58]，高通量筛选个性化药物组合，为精准治疗奠定基础。整合时序给药、靶向递送及个性化模型筛选，将推动靶向代谢–表观遗传网络的 OA 疗法从实验室走向临床。

6. 结论

OA 软骨退变的研究已进入“代谢–表观遗传协同调控”的新时代，其核心是“代谢异常与表观遗传

修饰的双向对话”。未来需通过联合干预(代谢酶–表观调控因子双靶点)、精准技术(纳米载体、CRISPR-dCas9)与类器官/人工智能(人类化模型、多组学分析)，解决代谢干预的“剂量–时空”控制与治疗矛盾，推动 OA 治疗从“对症”向“对因”转变。同时，基础转临床时需遵循“级联验证”，避免“粗暴干预”，确保治疗的安全性与有效性。

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