

代谢重编程与乳酸化修饰在椎间盘退变中的作用机制及治疗前景研究进展

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摘要 椎间盘退变是慢性腰痛的主要病理基础, 其发生发展与炎症反应、细胞外基质降解及细胞死亡密切相关。近年来研究发现, 椎间盘退变过程中存在显著的代谢重编程, 髓核细胞由氧化磷酸化向糖酵解代谢转变, 导致乳酸积累及酸性微环境形成。乳酸不仅可作为代谢产物, 还可通过蛋白质乳酸化修饰调控炎症反应、免疫细胞极化及程序性细胞死亡。蛋白质乳酸化可影响NF- κ B信号通路、NLRP3炎性小体活化及铁死亡等关键过程, 进而促进椎间盘退变进展。同时, 靶向代谢重编程及乳酸化修饰的干预策略在延缓椎间盘退变方面显示出潜在应用价值。该文系统综述代谢重编程与乳酸化修饰在椎间盘退变中的作用机制, 并探讨其潜在治疗前景, 为IVDD精准治疗提供理论依据。

关键词 椎间盘退变; 代谢重编程; 乳酸化; 糖酵解; 炎症反应; 细胞外基质

Research Progress on the Mechanisms and Therapeutic Prospects of Metabolic Reprogramming and Lactylation in Intervertebral Disc Degeneration

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Abstract IVDD (intervertebral disc degeneration) is the primary pathological basis of chronic low back pain, and its progression is closely associated with inflammatory responses, extracellular matrix degradation, and various forms of cell death. Recent studies have demonstrated that significant metabolic reprogramming occurs during IVDD, in which nucleus pulposus cells shift from oxidative phosphorylation to glycolysis, leading to lactate accumulation and formation of an acidic microenvironment. Lactate not only acts as a metabolic byproduct but also regulates inflammatory responses, immune cell polarization, and programmed cell death through protein lactylation. Lactylation has been shown to influence key processes, including the NF- κ B signaling pathway, NLRP3 inflammasome activation, and ferroptosis, thereby promoting the progression of IVDD. Meanwhile, therapeutic strategies targeting metabolic reprogramming and lactylation have demonstrated potential in delaying IVDD progression. This review systematically summarizes the roles of metabolic reprogramming and lactylation in IVDD and discusses their potential therapeutic implications, aiming to provide a theoretical basis for precision

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treatment of IVDD.

Keywords intervertebral disc degeneration; metabolic reprogramming; lactylation; glycolysis; inflammation; extracellular matrix

近年来研究表明,椎间盘退变(intervertebral disc degeneration, IVDD)不仅是炎症与基质降解的结果,还伴随显著的代谢重编程^[1]。髓核细胞在低氧及营养受限环境下由氧化磷酸化向糖酵解代谢转变,导致乳酸(lactic acid, LA)大量积累并形成酸性微环境。乳酸除作为代谢产物外,还可通过赖氨酸乳酸化(lysine lactylation)修饰调控炎症反应、免疫细胞极化及程序性细胞死亡等关键过程。越来越多研究发现,代谢重编程与乳酸化修饰之间形成“代谢-表观遗传”调控轴,在椎间盘退变发生发展中发挥重要作用。然而,目前关于代谢重编程-乳酸化修饰在IVDD中的系统性总结仍较为缺乏,尤其其对炎症反应、细胞死亡及细胞外基质(extracellular matrix, ECM)降解的整合机制尚不明确。因此,本文围绕代谢重编程-乳酸化修饰调控网络,对其在椎间盘退变中的作用机制及潜在治疗靶点进行综述。

1 椎间盘代谢微环境特点

椎间盘属于人体最大的无血管组织,营养主要依赖软骨终板弥散进入椎间盘内部,形成低氧、低营养及高乳酸的特殊代谢微环境^[2]。为适应此环境,椎间盘内髓核细胞进化出以糖酵解为主的代谢重编程,即缺氧适应,而非氧化磷酸化以维持内稳态。此过程不仅能够低氧条件下快速产生ATP以满足能量需求,而且其代谢副产物乳酸和H⁺离子造成的内源性酸性环境,有助于抵抗外部压力,并维持ECM中蛋白聚糖的含量,从而保持椎间盘的生物力学功能;同时髓核细胞内的线粒体数量相对较少,其形态和功能也发生了适应性改变^[3]。低氧诱导因子-1 α (hypoxia-inducible factor-1 α , HIF-1 α)在该过程中发挥关键作用,通过上调葡萄糖转运蛋白及糖酵解酶表达维持髓核细胞生存^[4]。在正常情况下,乳酸可通过单羧酸转运体(monocarboxylate transporter, MCT)排出细胞维持代谢平衡。然而随着椎间盘退变发生,终板钙化及营养扩散障碍导致乳酸清除能力降低,乳酸逐渐积累并形成酸性微环境。

2 代谢重编程在椎间盘退变中的作用

2.1 糖酵解增强

在IVDD过程中,髓核细胞代谢模式发生重编程,由氧化磷酸化向糖酵解转变。研究发现,退变椎间盘组织中糖酵解过程中的关键酶,如己糖激酶2(hexokinase 2, HK2)、磷酸果糖激酶-1(phosphofructokinase-1, PFK-1)、丙酮酸激酶M2(pyruvate kinase M2, PKM2)以及乳酸脱氢酶A(lactate dehydrogenase A, LDHA)表达明显上调,提示糖酵解水平提升^[5]。糖酵解增强导致乳酸大量生成,并通过降低细胞外pH值促进炎症反应及ECM降解。此外,糖酵解增强还可激活核因子 κ B(nuclear factor- κ B, NF- κ B)信号通路并促进炎症因子释放,从而加重椎间盘退变。PKM2作为关键代谢酶,还可进入细胞核调控炎症基因转录,进一步促进IVDD进展^[6]。

2.2 线粒体功能障碍

在长期退变应激下,椎间盘细胞的线粒体功能障碍,表现为线粒体膜电位下降、三羧酸循环关键酶活性降低、电子传递链复合体功能受损以及线粒体DNA突变积累,这是代谢重编程的重要表现^[7]。功能失调的线粒体不仅产能效率低下,无法满足细胞在应激状态下增加的能量需求,还会大量释放活性氧(reactive oxygen species, ROS),造成严重的氧化应激。过量的ROS会进一步损伤线粒体自身的膜结构和功能蛋白,同时攻击细胞内的其他大分子如DNA、蛋白质和脂质并激活NF- κ B及丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路,促进炎症反应及细胞凋亡^[8]。同时,在退变的椎间盘中,PINK1/Parkin介导的线粒体自噬通路受损,导致功能异常,产生活性氧的线粒体无法被及时清除而在细胞内堆积,最终诱导细胞凋亡、衰老或程序性坏死等多种死亡途径,进一步加剧椎间盘退变^[9]。

2.3 乳酸积累与酸性微环境

乳酸积累是代谢重编程的明确结果:IVDD过程中糖酵解增强而乳酸外排受阻,故乳酸在局部微环境内大量蓄积。现有充分证据表明,正常椎

间盘中乳酸浓度约为 5 mmol/L, 而退变椎间盘中可达 15 mmol/L 以上, 相应的组织 pH 值从 7.1 下降至 6.5, 甚至更低, 形成典型的酸性微环境^[10]。酸性环境本身即可直接抑制髓核细胞的代谢功能, 抑制蛋白聚糖及 II 型胶原的合成, 降低聚集蛋白聚糖 (aggrecan, ACAN) 的表达水平, 进而直接破坏 ECM 稳态^[11]。同时, 乳酸积累能主动、有效地激活炎症信号通路促进基质降解: 高浓度乳酸可上调基质降解酶基质金属蛋白酶-3 (matrix metalloproteinase-3, MMP-3)、基质金属蛋白酶-13 (matrix metalloproteinase-13, MMP-13) 及含血小板反应蛋白基序的解整合素及金属蛋白酶-5 (a disintegrin and metalloproteinase with thrombospondin motif-5, ADAMTS-5) 的表达, 同时抑制 SRY 相关高迁移率族盒蛋白 9 (SRY-related high-mobility group box 9, SOX9) 及 II 型胶原蛋白 $\alpha 1$ 链 (collagen type II $\alpha 1$ chain, COL2A1) 的表达, 最终导致 II 型胶原及蛋白聚糖的降解。乳酸还可通过激活 NF- κ B 及 MAPK 信号通路促进白细胞介素-1 β (interleukin-1 β , IL-1 β)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α) 及白细胞介素-6 (interleukin-6, IL-6) 等炎症因子的释放, 进一步放大炎症反应并加速椎间盘退变^[12]。酸性微环境可导致线粒体功能障碍并促进 ROS 生成, 进而诱导髓核细胞凋亡; 同时, 乳酸还可促进 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor family pyrin domain containing 3, NLRP3) 炎性小体激活并诱导细胞焦亡。此外, 乳酸介导的氧化应激可增强脂质过氧化作用并促进铁死亡发生^[13]。上述程序性细胞死亡通过抑制 ECM 合成和上调炎症介质表达, 形成“乳酸积聚-炎症反应-细胞死亡-ECM 降解”级联恶性循环, 导致椎间盘结构破坏与退行性病变的进行性加重。

3 乳酸化修饰的分子机制

3.1 乳酸化修饰概念

乳酸化修饰是近年来发现的新型翻译后修饰方式, 乳酸可作为底物在赖氨酸残基上形成乳酸化修饰, 从而调控基因表达。研究表明, 组蛋白乳酸化可调节炎症相关基因转录并参与免疫调控^[14]。

3.2 乳酸化调控炎症反应

乳酸化修饰可促进炎症因子表达。有研究提出 LA-组蛋白 H3 第 18 位赖氨酸乳酸化 (histone

H3 lysine 18 lactylation, H3K18la)-血小板反应蛋白-1 (thrombospondin-1, THBS1) 轴, 即乳酸含量减少导致 H3K18 位点乳酸化水平下降, 抑制促炎因子 THBS1 表达, 从而抑制炎症和减缓组织退变^[15]。这一发现揭示了乳酸不仅是代谢废物, 更是调控炎症基因表达的重要信号分子。另有研究发现, 乳酸可通过组蛋白乳酸化促进 IL-1 β 及 TNF- α 表达, 并调节巨噬细胞极化状态^[16]。此外, 乳酸化还可增强 NF- κ B 信号通路活性, 从而促进炎症反应并加速椎间盘退变。

3.3 乳酸化调控程序性细胞死亡

乳酸化修饰还参与调控焦亡及铁死亡的过程。乳酸可促进 NLRP3 炎性小体激活并诱导细胞焦亡, 同时通过上调 ROS 水平及脂质过氧化程度促进铁死亡发生^[17]。有研究进一步发现, 乳酸诱导酰基辅酶 A 合成酶长链家族成员 4 (acyl-CoA synthetase long-chain family member 4, ACSL4) 的转录激活及蛋白乳酸化, 促进铁死亡, 表明乳酸化调控不仅限于组蛋白, 也可作用于非组蛋白, 进而影响细胞死亡途径^[18]。乳酸还通过降低去乙酰化酶沉默信息调节因子 3 (sirtuin-3, SIRT3) 表达水平, 间接促进 ACSL4 乳酸化, 形成复杂的调控网络。

3.4 非组蛋白乳酸化

乳酸化修饰除作用于组蛋白外, 还可调控多种非组蛋白功能蛋白。研究发现, 乳酸可诱导 ACSL4 发生乳酸化修饰, 促进脂质过氧化并触发铁死亡^[19]。此外, 乳酸化还可调控代谢酶活性、炎症相关转录因子及线粒体功能蛋白等的表达, 从而影响细胞能量代谢及氧化应激水平。非组蛋白乳酸化进一步扩展了乳酸在椎间盘退变中的调控范围, 使代谢重编程-表观遗传调控-程序性细胞死亡之间形成更复杂的调控网络。

4 代谢重编程-乳酸化-细胞死亡-ECM 调控网络

代谢重编程导致糖酵解增强、乳酸大量积累, 这既有利于形成酸性微环境, 又可通过组蛋白及非组蛋白乳酸化修饰调控炎症相关基因表达。乳酸化能增强 NF- κ B 信号通路活性, 上调 IL-1 β 、TNF- α 及 IL-6 的表达, 从而形成持续性炎症微环境。更重要的是, NF- κ B 可介导 NLRP3 炎性小体的启动信号, 促成 Caspase-1 激活及细胞焦亡的发生^[20]。炎症因

子可上调MMP-3、MMP-13及ADAMTS-5的表达,同时抑制SOX9及COL2A1的表达,导致II型胶原及蛋白聚糖降解。此外,乳酸积累还可通过增强氧化应激反应来参与铁死亡调控:高乳酸环境诱导线粒体功能障碍,ROS生成量增多,脂质过氧化加剧,谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)表达被抑制,故可诱发铁死亡。铁死亡过程中释放的脂质过氧化产物及损伤相关分子模式(damage-associated molecular patterns, DAMPs)可进一步激活免疫反应并放大炎症信号,形成正反馈循环。焦亡与铁死亡释放的炎症介质及损伤相关分子模式进一步放大炎症反应并促进基质降解。

正常髓核ECM主要由II型胶原及蛋白聚糖构成,维持椎间盘含水量及生物力学功能。代谢重编程导致乳酸积累及炎症微环境形成,可显著打破ECM代谢平衡。研究表明,乳酸可通过激活NF- κ B及MAPK信号通路上调MMP-3、MMP-13及ADAMTS-5表达。其中MMP-13主要降解II型胶原,而ADAMTS-5是降解蛋白聚糖的关键酶,两者共同导致ECM结构破坏及椎间盘含水量下降^[21]。此外,乳酸诱导的炎症反应也可促进ECM降解。IL-1 β 及TNF- α 可抑制SOX9及COL2A1表达,从而抑制II型胶原及蛋白聚糖合成,同时促进基质降解酶表达,进一步加剧基质破坏^[22]。酸性微环境还可直接抑制髓核细胞合成功能并降低聚集蛋白聚糖表达水平,加速ECM降解进程。

细胞凋亡及铁死亡导致髓核细胞数量减少,使ECM合成能力下降;焦亡释放的IL-1 β 及HMGB1可进一步激活炎症反应并增强MMPs表达^[23]。随着ECM持续降解,纤维环结构破裂及终板损伤逐渐加重,上述损伤最终导致椎间盘高度降低及力学功能丧失,推动椎间盘退变进展。

因此,代谢重编程导致的乳酸积累不仅可以通过乳酸化修饰调控炎症基因表达,还可以通过NF- κ B/NLRP3轴诱导细胞焦亡,同时通过氧化应激促进铁死亡。上述过程相互交织,形成“代谢重编程-乳酸化-炎症-程序性细胞死亡”调控网络,持续放大炎症反应并促进椎间盘退变及椎间盘源性疼痛发生。

基于上述“代谢重编程-乳酸化-炎症-程序性细胞死亡”调控网络的逻辑框架,本文进一步构建代谢重编程-乳酸化-细胞死亡-ECM调控网络示意

图(图1),旨在系统阐明代谢重编程在IVDD及椎间盘源性疼痛发生发展中的核心枢纽作用。

5 靶向代谢重编程的治疗前景

目前学界对代谢重编程及乳酸化修饰在IVDD中的作用已有十分明确的认识,因此靶向代谢调控已经成为延缓IVDD进展十分有前景的治疗策略。干预糖酵解、乳酸生成及乳酸化修饰等关键环节,能够改善炎症微环境、减少程序性细胞死亡并维持ECM稳态。

5.1 抑制糖酵解

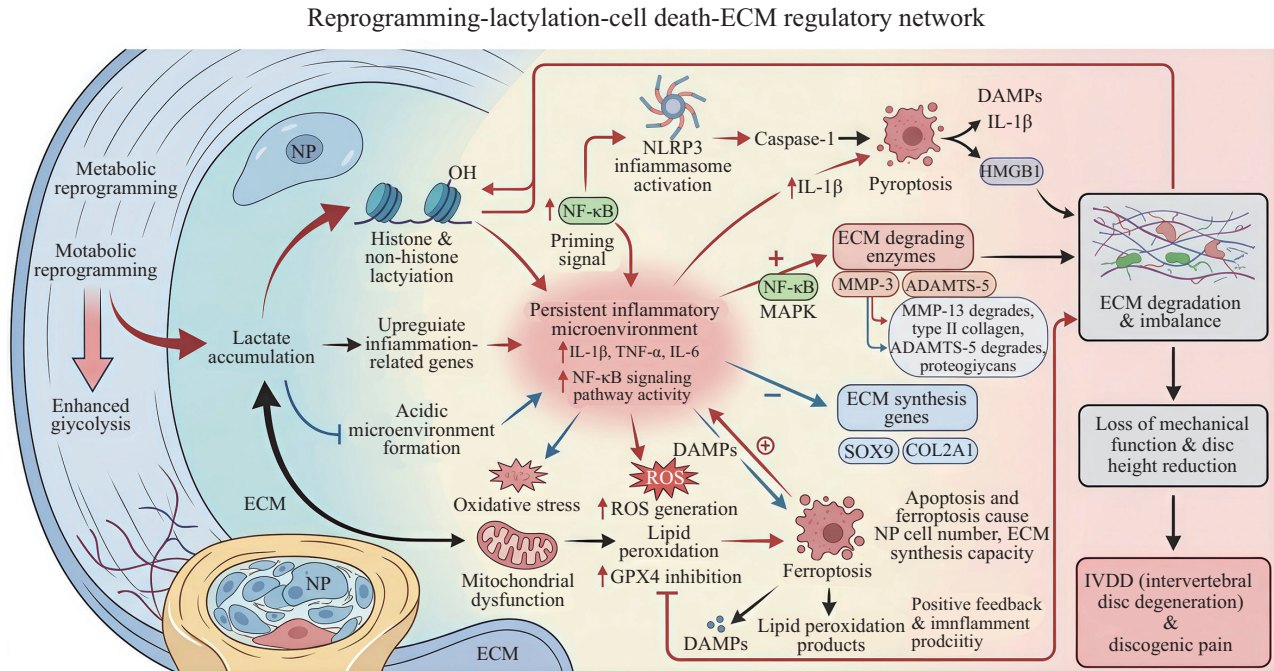
糖酵解增强是乳酸积累的主要来源,因此抑制糖酵解可减少乳酸生成并减轻炎症反应。研究表明,糖酵解抑制剂2-脱氧-D-葡萄糖(2-deoxy-D-glucose, 2-DG)可抑制己糖激酶活性,从而抑制乳酸生成并减轻炎症反应^[24]。此外,抑制PKM2或LDHA表达亦可下调糖酵解水平,抑制ROS生成和髓核细胞凋亡。相关研究发现,阻断糖酵解可抑制IL-1 β 诱导的MMPs表达并改善ECM代谢,提示糖酵解抑制剂在延缓椎间盘退变方面具有潜在应用价值^[25]。

5.2 调控乳酸代谢

乳酸积累是形成酸性微环境的重要因素,因此调节乳酸生成或转运可改善椎间盘微环境。乳酸跨膜转运主要依赖单羧酸转运体(MCT1和MCT4),抑制MCT介导的乳酸外排可调节局部乳酸浓度并减轻炎症反应^[26]。研究显示,调控乳酸代谢可降低NF- κ B信号通路活性并减少炎症因子释放。此外,改善线粒体功能及增强氧化磷酸化亦可抑制乳酸生成,从而延缓IVDD进展。既往研究显示,通过抗氧化干预或线粒体功能保护纠正能量代谢紊乱的干预手段,不仅能够减少髓核细胞凋亡,同时可促进ECM的合成^[27]。

5.3 靶向乳酸化修饰

乳酸化修饰是连接代谢重编程与炎症反应的重要表观遗传机制。抑制组蛋白乳酸化可降低炎症基因表达水平并抑制细胞死亡。研究发现,乳酸化修饰可调控巨噬细胞极化并增强炎症反应,而阻断乳酸化过程可抑制IL-1 β 及TNF- α 表达。此外,乳酸化还与NLRP3炎性小体激活及铁死亡相关,调控乳酸化水平可同时影响多种程序性细胞死亡方式^[28]。因此,靶向乳酸化修饰可能成为IVDD治疗的新方向。



代谢重编程促进糖酵解增强及乳酸积累, 乳酸通过诱导组蛋白/非组蛋白乳酸化修饰及形成酸性微环境, 激活炎症相关基因表达和NF-κB信号通路, 促进持续性炎症微环境形成。同时, 乳酸积累诱导线粒体功能障碍及ROS生成量增加, 进一步触发NLRP3-Caspase-1介导的细胞焦亡及ROS/脂质过氧化相关铁死亡。焦亡和铁死亡释放的DAMPs进一步放大炎症反应, 形成正反馈调控环路。炎症信号通过NF-κB/MAPK通路促进MMP-3、MMP-13及ADAMTS-5等ECM降解酶表达, 并抑制SOX9、COL2A1等ECM合成相关酶的表达, 最终导致ECM合成与降解失衡, 促进椎间盘结构破坏及退变进展。红色箭头(+/⊕)表示促进/激活作用; +: 普通促进/激活; ⊕: 正反馈、增强性促进; 蓝色“T”形线(-)表示抑制作用; “T”字型箭头表示抑制/阻断作用; 黑色箭头表示过程传递/病理进展; 向上的箭头表示上调。

Metabolic reprogramming enhances glycolysis and lactate accumulation. Lactate induces histone/non-histone lactylation modifications and forms an acidic microenvironment, thereby activating the expression of inflammation-related genes and the NF-κB signaling pathway to facilitate the establishment of a persistent inflammatory microenvironment. Meanwhile, lactate accumulation triggers mitochondrial dysfunction and elevated ROS production, which further initiates NLRP3-Caspase-1-mediated pyroptosis as well as ROS/lipid peroxidation-associated ferroptosis. DAMPs released during pyroptosis and ferroptosis further amplify inflammatory responses, constituting a positive feedback regulatory loop. Inflammatory signals upregulate the expression of ECM-degrading enzymes including MMP-3, MMP-13 and ADAMTS-5 via the NF-κB/MAPK pathway, while suppressing ECM synthesis-related proteins such as SOX9 and COL2A1. This ultimately leads to an imbalance between ECM synthesis and degradation, accelerating intervertebral disc structural damage and degeneration progression. Red arrows (+/⊕) indicate promotion/activation; +: promotion or activation; ⊕: positive-feedback, enhanced promotion; blue T-shaped lines (-) indicate inhibitory effects; “T”-shaped arrows indicate inhibition/blockade; black arrows indicate process transmission/pathological progression; upward arrows indicate upregulation.

图1 代谢重编程-乳酸化-细胞死亡-ECM调控网络示意图(图片部分来源于Google Gemini, 由BioRender网站支持修改)

Fig.1 Schematic diagram of the metabolic reprogramming-lactylation-cell death-ECM regulatory network (partial image materials derived from Google Gemini, modified with support from BioRender)

5.4 靶向免疫代谢重编程

近年来研究发现, 代谢重编程不仅发生于髓核细胞, 还参与调控椎间盘免疫微环境。衰老髓核细胞可诱导巨噬细胞向M1型极化, 而M1巨噬细胞分泌炎症因子又促进髓核细胞代谢重编程及乳酸积累, 形成恶性循环^[29]。研究表明, 人诱导多能干细胞来源的间充质干细胞外泌体可通过递送miR-100-5p抑制mTORC1信号通路, 降低巨噬细胞糖酵解水平并促进M2型极化, 从而减轻炎症反应并延缓IVDD进展。该研究提示靶向免疫细胞代谢重编程可作为代谢-乳酸化调控网络的重要干预策略。

6 总结与展望

代谢重编程是椎间盘退变发生发展的重要机制, 髓核细胞由氧化磷酸化向糖酵解转变导致乳酸积累并形成酸性微环境。乳酸不仅作为代谢产物, 还可通过乳酸化修饰调控炎症反应及程序性细胞死亡, 从而促进椎间盘退变。代谢重编程、乳酸化修饰与炎症反应之间形成复杂调控网络, 通过NF-κB信号通路、NLRP3炎性小体及铁死亡等途径持续放大炎症反应并破坏ECM稳态。未来研究应重点关注以下几个方面: 第一, 进一步阐明代谢重编程在不同退变阶段中的作用差异, 明确关键调控节点; 第二,

深入研究乳酸化修饰在髓核细胞、免疫细胞及终板细胞中的作用机制;第三,探索靶向糖酵解、乳酸代谢及乳酸化修饰的联合治疗策略;第四,结合单细胞RNA测序及空间转录组学技术解析椎间盘内细胞异质性及细胞间通信网络;第五,推动代谢调控相关药物的体内研究及临床转化。

综上所述,靶向代谢重编程及乳酸化修饰为椎间盘退变的精准治疗提供了新的研究方向,未来多组学技术与机制研究相结合的研究,有望为IVDD的早期干预及个体化治疗提供新的理论依据和潜在靶点。

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