糖代谢重编程及其靶向治疗药物在炎症相关疾病中的作用

未 怡[1], 江小慢[1], 夏仕林[1], 许 静[1], 李 雅[1], 邓 然[2], 王 言[1], 吴 虹[1*]

(1. 安徽中医药大学药学院, 新安医学教育部重点实验室, 中药研究与开发安徽省重点实验室, 安徽 合肥 230012;
2. 安徽中医药大学中西医结合学院, 安徽 合肥 230012)

摘要: 细胞在炎性微环境影响下发生糖代谢重编程, 使其主要供能方式由氧化磷酸化转变为有氧糖酵解, 该过程参与炎症相关疾病发生发展的各个阶段。糖代谢重编程不仅改变单个细胞的代谢模式, 而且打破了机体微环境的代谢稳态, 进一步促进细胞有氧糖酵解, 为炎症相关疾病的恶性进展提供有利条件。有氧糖酵解的相关代谢酶、转运蛋白、代谢产物等均为关键信号分子, 药物通过靶向这些特异性强的关键分子, 抑制有氧糖酵解从而发挥治疗作用。本文围绕糖代谢重编程对炎症相关肿瘤、类风湿关节炎、阿尔茨海默病等炎症相关疾病发生发展的影响以及药物靶向糖代谢重编程对疾病的治疗作用展开综述。

关键词: 糖代谢重编程; 有氧糖酵解; 炎症相关疾病; 炎性微环境; 靶向治疗

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The role of glucose metabolism reprogramming and its targeted therapeutic agents in inflammation-related diseases

WEI Yi[1], JIANG Xiao-man[1], XIA Shi-lin[1], XU Jing[1], LI Ya[1], DENG Ran[2], WANG Yan[1], WU Hong[1*]

(*1. Key Lab of Xin'an Medicine, Ministry of Education, Anhui Province Key Laboratory of Research and Development of Chinese Medicine, School of Pharmacy, Anhui University of Chinese Medicine, Hefei 230012, China; 2. School of Integrated Traditional and Western Medicine, Anhui University of Chinese Medicine, Hefei 230012, China*)

Abstract: Cells undergo glucose metabolism reprogramming under the influence of the inflammatory microenvironment, changing their primary mode of energy supply from oxidative phosphorylation to aerobic glycolysis. This process is involved in all stages of inflammation-related diseases development. Glucose metabolism reprogramming not only changes the metabolic pattern of individual cells, but also disrupts the metabolic homeostasis of the body microenvironment, which further promotes aerobic glycolysis and provides favourable conditions for the malignant progression of inflammation-related diseases. The metabolic enzymes, transporter proteins, and metabolites of aerobic glycolysis are all key signalling molecules, and drugs can inhibit aerobic glycolysis by targeting these specific key molecules to exert therapeutic effects. This paper reviews the impact of glucose metabolism reprogramming on the development of inflammation-related diseases such as inflammation-related tumours, rheumatoid arthritis and Alzheimer's disease, and the therapeutic effects of drugs targeting glucose metabolism reprogramming on these diseases.

Key words: glucose metabolism reprogramming; aerobic glycolysis; inflammation-related disease; inflammatory microenvironment; targeted therapy

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*通讯作者 Tel: 13485606565, E-mail: wuhongprof@aliyun.com

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糖代谢重编程是指细胞为应对微环境的变化从而调整葡萄糖代谢模式, 以满足激增的生物能量和生物合成需求[1]。葡萄糖作为细胞主要的生长燃料, 正常细胞在氧气充足条件下通过氧化磷酸化 (oxidative phosphorylation, OXPHOS) 将其转化为H_2O和CO_2, 并产生ATP。在炎症相关疾病中, 大量炎性细胞恶性增殖形成的炎性微环境是诱发糖代谢重编程的重要因素之一, 糖代谢重编程的发生会改变微环境中细胞的能量供应方式, 进而影响疾病进程[2] (图1)。异常增殖的细胞即使在有氧条件下也会优先选择将葡萄糖转化为丙酮酸产生乳酸, 并伴有少量ATP生成, 这种低能代谢方式由Otto Warburg首次观察到, 被称为有氧糖酵解/Warburg效应[3]。虽然糖代谢重编程的供能效率低, 但其为细胞快速提供生物大分子材料和高能代谢前体物质。磷酸戊糖途径 (pentose phosphate pathway, PPP) 作为糖代谢另一种旁路途径, 在生物大分子合成过程中也具有重要作用。PPP源于糖酵解的第一个产物6-磷酸葡萄糖, 该途径为细胞生存和增殖提供所需的核苷酸与NADPH, 并将碳分流回糖酵解途径[4]。鉴于糖代谢重编程在炎症相关疾病发生发展中的重要作用, 近年来相关靶向治疗药物的研发受到广泛关注。本文主要介绍糖代谢重编程对炎症相关疾病发生发展的影响、有氧糖酵解过程中的关键信号分子及其作用机制, 并梳理了靶向有氧糖酵解关键分子的化合物或药物, 以期从糖代谢重编程视角为揭示该类疾病的机制和治疗策略提供依据。

1 糖代谢重编程在炎症相关疾病中的作用

1.1 糖代谢重编程与炎症相关肿瘤 慢性炎症导致约20%恶性肿瘤的发生发展, 如结肠癌、肝癌、胃癌等。多项研究表明, 慢性炎症可以通过STAT3与缺氧诱导因子-1α (hypoxia inducible factor-1α, HIF-1α) 等相关信号通路, 上调其下游代谢酶的表达, 引起糖酵解增加从而触发癌症发展的级联反应。在慢性结肠炎小鼠模型中, 促炎因子IL-6通过激活STAT3/c-Myc信号轴, 上调糖酵解关键酶的表达, 增加有氧糖酵解水平, 导致结肠炎相关癌症的发生[5]。肝癌细胞中积累的

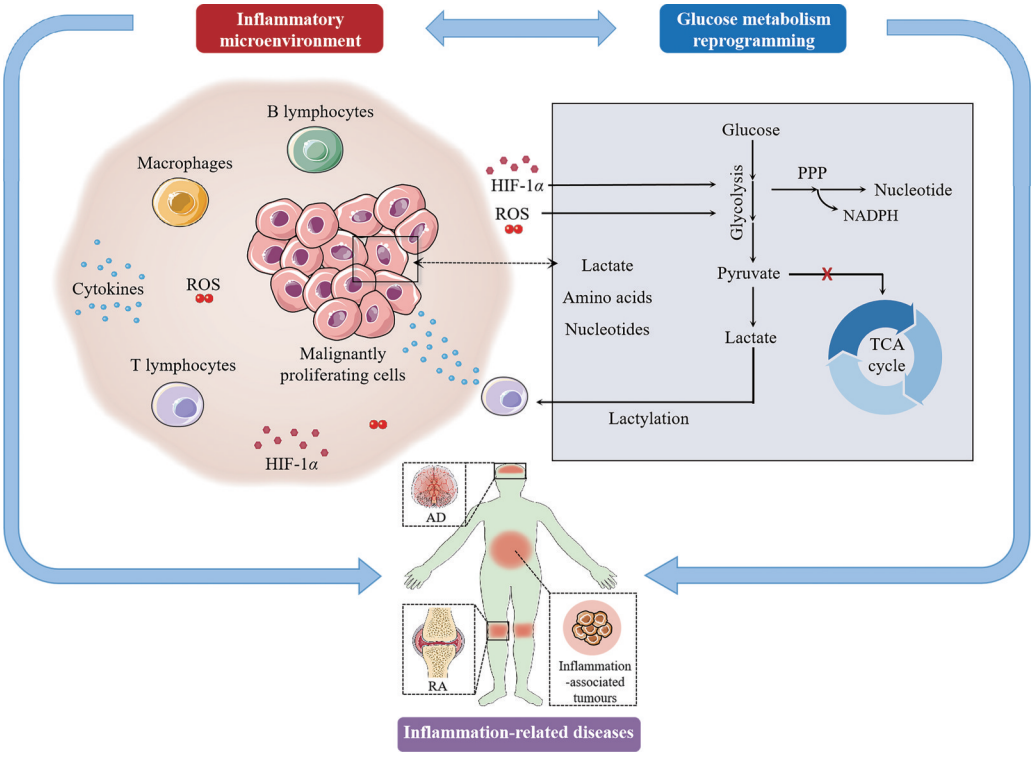

Figure 1 The link between the inflammatory microenvironment and glucose metabolism reprogramming in inflammation-related diseases. The inflammatory microenvironment includes malignantly proliferating cells, immune cells, and various signalling molecules, etc. HIF-1α and ROS, as key signalling molecules, directly affect glycolysis and PPP and other glucose metabolic pathways. Cellular metabolites such as lactate, amino acids and nucleotides can act as signalling molecules to regulate inflammatory responses in the microenvironment and can also be recycled by cells back into metabolic pathways. Among them, lactate is able to influence the stability and function of regulatory T cells through lactylation. The interplay between the inflammatory microenvironment and glucose metabolism reprogramming plays a key role in the development and progression of inflammation-related diseases. HIF-1α: Hypoxia inducible factor-1α; ROS: Reactive oxygen species; PPP: Pentose phosphate pathway; TCA: Tricarboxylic acid; AD: Alzheimer's disease; RA: Rheumatoid arthritis

HIF-1α可与YAP结合, 直接激活代谢酶转录, 加速有氧糖酵解, 促进肝癌生长和转移[6]。因此, 糖代谢重编程是炎症相关肿瘤恶性发生发展的关键。糖代谢重编程为肿瘤细胞的异常增殖不仅提供了能量和必需的代谢中间体, 而且创造了有利的肿瘤微环境 (tumor microenvironment, TME)。TME是由肿瘤细胞、免疫细胞和肿瘤基质等组成的复杂细胞环境[7]。肿瘤相关成纤维细胞 (cancer-associated fibroblasts, CAFs) 是一种永久激活的成纤维细胞, 其发生反向Warburg效应, 即CAFs经肿瘤细胞诱导进行有氧糖酵解, 产生的代谢物"喂养"肿瘤细胞并支持其进行OXPHOS, 促进肿瘤的生长和转移[8]。肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 是重要的先天性免疫细胞, 具有经典激活M1和交替激活M2两个表型。研究表明, TAMs的糖代谢重编程影响其表型的功能重编程。M1型主要利用有氧糖酵解进行供能; M2型则选择OXPHOS作为主要的能量代谢途径, 发挥促肿瘤作用[9]。适应性免疫的重要效应细胞—T细胞和B细胞在激活的状态下倾向于有氧糖酵解进行供能, 满足细胞增殖和效应功能增加的需求。而肿瘤细胞通过多种途径阻碍免疫细胞获取营养物质, 破坏免疫细胞的代谢稳态和功能, 帮助自身实现免疫逃逸[10]。综上, 在炎症相关肿瘤中, 肿瘤细胞与免疫细胞的糖代谢重编程对疾病的发生发展具有重要意义。

1.2　糖代谢重编程与类风湿关节炎　类风湿关节炎 (rheumatoid arthritis, RA) 作为典型的炎症性自身免疫性疾病, 其病理特征为关节滑膜炎性增生和功能不全的微血管生成, 导致类肿瘤样的病理产物血管翳的产生[11]。随着RA病程加剧, 关节滑膜细胞的葡萄糖摄取量增加, 糖酵解速率升高, 为免疫细胞的活化和效应细胞的增殖提供能量和营养物质[12]。RA的糖代谢重编程和炎症反应由多个信号通路共同调控。有研究证实, JAK/STAT通路介导了RA发病机制中炎症和细胞糖代谢之间复杂的相互作用, 该机制可能是通过NF-κB、HIF-1α和PI3K的双向交互作用实现的[13]。转录因子NF-κB作为炎症过程的中枢介质, 其磷酸化会促进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, 提高成纤维样滑膜细胞 (fibroblast-like synoviocytes, FLSs) 的有氧糖酵解活性, 促进FLSs增殖和侵袭[14]。AMPK是细胞能量状态的重要传感器, 在RA小鼠模型中, 激活的AMPK能够抑制巨噬细胞的糖酵解水平, 促使巨噬细胞转变为抑炎表型[15]。与肿瘤细胞相似, 滑膜细胞 (主要由FLSs和巨噬样滑膜细胞组成) 与免疫细胞等构成滑膜炎性微环境。FLSs具有维持关节稳态和控制炎症的重要作用。由于生物合成需求增加, FLSs的葡萄糖代谢向有氧糖酵解偏移, 导致RA炎症反应和关节损伤加重[16]。在RA中, 巨噬细胞M1和M2表型的代谢活性与炎症相关肿瘤中相反。M1型的代谢向有氧糖酵解和PPP转变且具有促炎作用, 相反, M2型表现为增强的OXPHOS和脂肪酸氧化, 发挥抗炎作用。在炎性微环境下, FLSs和巨噬细胞的相互作用进一步诱导糖代谢重编程并增加巨噬细胞的生存能力, 加剧RA的慢性炎症[17]。$CD4^+$ T细胞作为RA免疫异常的关键驱动细胞, 使葡萄糖代谢从糖酵解途径分流到PPP以生成细胞生长前体物质, 从而发挥促炎效应功能[18]。因此, 靶向RA中滑膜炎性微环境的糖代谢重编程可能成为治疗RA的新策略。

1.3　糖代谢重编程与阿尔茨海默病　阿尔茨海默病 (Alzheimer's disease, AD) 是一种常见的神经退行性疾病, 其主要特征为细胞外β样淀粉蛋白 (amyloid-beta, Aβ) 斑块形成以及慢性神经炎症等。已有研究证明, p38 MAPK作为一种响应细胞外压力刺激 (如神经炎症) 的反应元件, 其活性在AD患者大脑中升高。p38 MAPK能够调控与AD发病机制相关的多个事件, 如Aβ斑块诱导的神经损伤、神经炎症等。近期有研究报道, 小胶质细胞的糖代谢重编程能够通过p38 MAPK通路, 诱导促炎细胞因子IL-1β和TNF-α释放, 加剧神经炎症[19]。小胶质细胞是中枢神经系统固有的免疫细胞, 负责监测环境以维持大脑的稳态。在AD中, Aβ斑块会诱发小胶质细胞持续激活和增殖并产生炎症表型, 该过程中细胞代谢转变为有氧糖酵解, 导致细胞吞噬能力降低, 加剧神经变性[20]。激活的小胶质细胞反过来利用有氧糖酵解, 诱导促炎因子慢性释放, 导致炎症级联反应[21]。星形胶质细胞在AD的发病机制中也具有重要作用, 其为神经元提供营养和代谢支持, 广泛参与大脑的能量代谢。星形胶质细胞是发生高度糖酵解的细胞, 其糖代谢重编程是AD进行性功能障碍的基础[22]。星形胶质细胞摄取并储存大量聚集的Aβ沉积物, 导致糖酵解功能失调, 打破了神经元能量代谢稳态, 加速AD病程[23]。因此, 靶向上述两种胶质细胞的有氧糖酵解水平可能有助于预防或降低AD的风险。

1.4　糖代谢重编程与其他炎症相关疾病　研究发现, 适应性免疫细胞的糖代谢重编程对系统性红斑狼疮 (systemic lupus erythematosus, SLE) 的发病机制至关重要。在SLE患者体内, T细胞通过糖代谢重编程诱导辅助性T细胞17活化, 进而增强自身免疫性[24]。同时, 患者体内增强的糖酵解还支持功能性调节B细胞的生长和功能, 促进其分泌促炎因子[25]。在糖尿病肾病中, 肾巨噬细胞的糖酵解增加进而增加细胞中炎症

和纤维化基因表达, 诱导肾纤维化[26]。除上述疾病, 越来越多的研究证明糖代谢重编程在溃疡性结肠炎、过敏性哮喘和多发性硬化症等炎症相关疾病中也发挥重要作用。

2 有氧糖酵解及其过程中的关键信号分子

糖酵解过程涉及一系列的酶促反应 (图2)。糖酵解主要过程为葡萄糖经葡萄糖转运蛋白 (glucose transporters, GLUTs) 进入细胞质, 通过己糖激酶 (hexokinase, HK) 催化为6-磷酸葡萄糖; 6-磷酸葡萄糖经过磷酸果糖激酶1 (phosphofructo-kinase 1, PFK1) 和丙酮酸激酶 (pyruvate kinase, PK) 等代谢酶转化为丙酮酸。有氧糖酵解是指即使在有氧的条件下, 丙酮酸经过乳酸脱氢酶A (lactate dehydrogenase A, LDHA) 转化为乳酸, 而不是转化为乙酰辅酶A, 进入线粒体进行三羧酸循环 (tricarboxylic acid cycle, TCA cycle)。代谢终产物乳酸通过单羧酸盐转运蛋白 (monocarboxylate transporters, MCTs) 在细胞间运输并发挥作用。在炎性微环境中, 有氧糖酵解过程的代谢酶、转运蛋白、代谢产物以及HIF-1α与活性氧 (reactive oxygen species, ROS) 等通过调控糖代谢过程进而影响炎症相关疾病的发生发展。

2.1 代谢酶 HK是催化葡萄糖进行有氧糖酵解的第一个限速酶, 产物为6-磷酸葡萄糖; 其4种同工酶 (HK1～4) 具有不同的催化活性, 其中HK2是最活跃的同工酶。HK2通过调控多个免疫相关信号通路, 驱动免疫细胞的有氧糖酵解, 促进炎症反应, 参与炎症相关疾病的发生发展。乙型肝炎病毒X蛋白通过NF-κB p65/HK2途径诱导有氧糖酵解。有氧糖酵解产生的过量乳酸激活PI3K/Akt信号通路, 促进肝细胞恶性增殖, 导致肝细胞癌变[27]。HK2在RA FLSs中特异性高表达, 并结合mTOR促进细胞自噬, 过度激活的自噬降低了FLSs凋亡的频率[28]。在AD小鼠大脑中, 小胶质细胞中的HK2受到抑制后, 显著促进细胞的吞噬作用, 减轻认知功能障碍[29]。可见, HK2可作为炎症相关疾病的选择性代谢靶标。

磷酸果糖激酶-2/果糖-2,6-二磷酸酶3 (phospho-fructokinase-2/fructose-2,6-bisphosphatase 3, PFKFB3) 催化6-磷酸果糖不可逆地转化为2,6-二磷酸果糖。2,6-二磷酸果糖作为PFK1的变构激活剂, 促进PFK1将6-磷酸果糖转化为1,6-二磷酸果糖。PFKFB3在肠

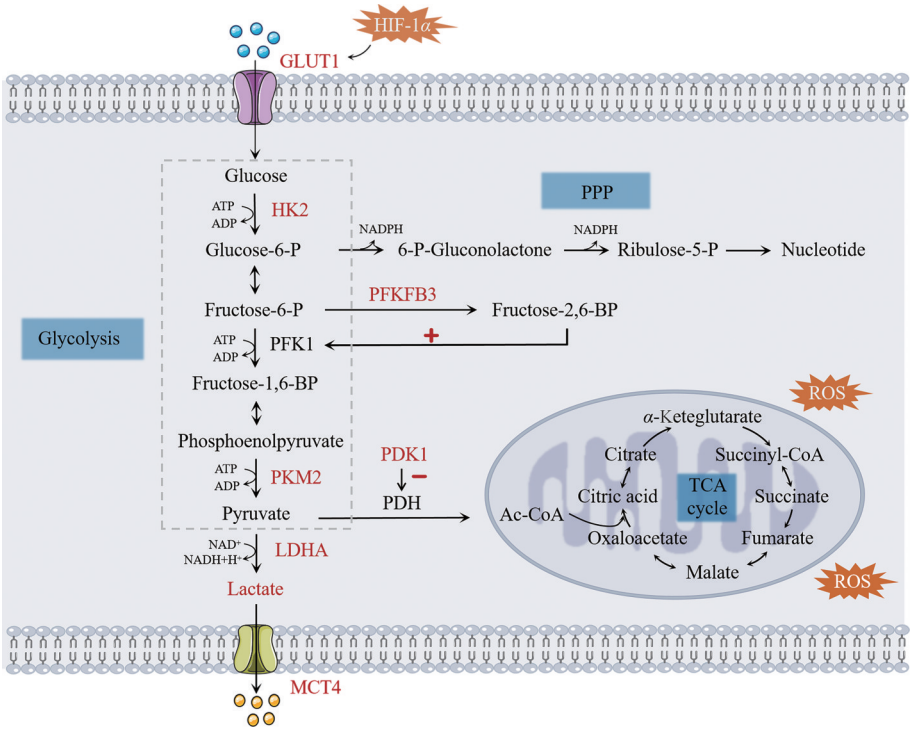

Figure 2 Key signalling molecules involved in cellular glucose metabolism (metabolic enzymes, transporter proteins, metabolites, etc.). Glucose enters the cytoplasm *via* GLUTs and is converted to pyruvate by a variety of metabolic enzymes. Aerobic glycolysis converts pyruvate to lactate *via* LDHA without entering the mitochondria for the TCA cycle even under aerobic conditions. PPP is derived from the first product of glycolysis, glucose 6-phosphate, which ultimately generates nucleotides required for cell survival and proliferation. ＋ denotes promotion and － denotes inhibition. GLUTs: Glucose transporters; HK2: Hexokinase 2; PFK1: Phosphofructokinase 1; PFKFB3: Phosphofructokinase-2/fructose-2,6-bisphosphatase 3; PKM2: Pyruvate kinase M2; PDH: Pyruvate dehydrogenase; PDK1: Pyruvate dehydrogenase kinase 1; LDHA: Lactate dehydrogenase A; MCT4: Monocarboxylate transporter 4

上皮细胞过表达, 通过上调p65磷酸化水平, 促进IL-1β和TNF-α表达, 导致结肠炎相关癌症的发生[30]。同时, PFKFB3增加HIF-1α表达, 两者间的正反馈回路诱导肿瘤细胞的耐药性[31]。研究表明, PFKFB3参与AD的发病机制, 其表达降低导致星形胶质细胞易受Aβ毒性的影响, 进而促进Aβ积累和斑块形成[32]。PFKFB3还参与内皮细胞增殖, 通过驱动有氧糖酵解致使血管出芽, 影响尖端与茎细胞的形成。肿瘤中激活的NF-κB信号通路能够增强PFKFB3介导的有氧糖酵解, 刺激内皮细胞并促进肿瘤血管生成[33]。

PK为糖酵解过程的末端限速酶, 催化磷酸烯醇式丙酮酸转化为丙酮酸。PK具有PKL、PKR、PKM1和PKM2四种亚型, 并根据细胞类型而分布不同。其中PKM2主要在肿瘤细胞与增殖细胞中表达, 其具有不同生物效应的二聚体与四聚体两种状态。四聚体PKM2具有较高的丙酮酸激酶活性, 促进糖酵解; 二聚体PKM2代谢活性较低, 但能易位至细胞核并参与基因转录[34]。多项研究证实了PKM2通过代谢或非代谢途径参与炎症相关疾病的发生发展。PKM2所在的信号通路mTOR/PKM2和STAT3/c-Myc共同构成调控肿瘤有氧糖酵解的分子网络, 并调节酸性微环境, 促进肿瘤细胞增殖[35]。活化的二聚体PKM2磷酸化STAT3, 进而促进IL-6和IL-1β产生; 另一方面促进辅助性T细胞17细胞分化, 介导全身炎症[36,37]。

丙酮酸脱氢酶激酶 (pyruvate dehydrogenase kinase, PDK) 是糖酵解关键酶丙酮酸脱氢酶 (pyruvate dehydrogenase, PDH) 的调控酶, 具有PDK1～4四种亚型。其中PDK1是PDH的抑制酶, 其阻碍丙酮酸脱羧生成乙酰辅酶A参与三羧酸循环, 调控细胞糖代谢重编程。在肿瘤中, HIF-1α上调原癌基因FOXM1表达, FOXM1可直接与PDK1的启动子区结合, 增加PDK1在转录水平上的表达, 并导致PDH在丝氨酸293处磷酸化, 抑制其活性, 增强有氧糖酵解进而促进肿瘤细胞增殖[38]。研究发现, PDK1除了发挥糖酵解酶的典型作用外, 还可以将PKM2和抗凋亡蛋白 (如Bcl-2/Bcl-xL) 锚定在线粒体膜上, 从而增强肿瘤细胞对凋亡刺激的抵抗[39]。

乳酸脱氢酶 (lactate dehydrogenase, LDH) 是一种由A和B亚型组成的四聚体酶。在有氧糖酵解的最后一步, LDHA可催化丙酮酸向乳酸转化, 而LDHB可使乳酸转化为丙酮酸。LDHA是许多恶性肿瘤的标志物, 并通过多种机制参与肿瘤进展。LDHA可直接与Wnt/β-catenin途径激活的癌基因Myc结合, 增强有氧糖酵解, 加速肿瘤细胞增殖和转移[40]。LDHA的表达和功能也受到翻译后修饰作用的调控。LDHA在K155位点的琥珀酰化提高了其活性, 从而增强了肿瘤细胞的葡萄糖摄取和乳酸积累, 导致肿瘤恶性进展[41]。在RA $CD8^+$ T细胞亚群中, LDHA过表达并通过促进$CD8^+$ T细胞增殖, 发挥促炎作用[42]。已有研究证实, 靶向LDHA抑制有氧糖酵解可显著影响疾病发展, 且不会对正常细胞产生损伤[43]。

2.2　转运蛋白　GLUT1是一种介导葡萄糖转运的关键蛋白。在肿瘤中, GLUT1促使癌基因表达并通过非编码RNA调节TME, 导致肿瘤恶性发展和转移[44,45]。GLUT1在RA患者滑膜组织中高表达, 其通过与HIF-1α靶向结合共同影响RA病理发展[46]。

MCT1和MCT4是介导有氧糖酵解产物乳酸运输的关键共生体。MCT1双向运输乳酸, 并同时参与有氧糖酵解和OXPHOS, 且其表达水平与HIF-1α水平呈相关性[47]。MCT4则参与乳酸排出胞外的过程, 维持细胞内碱外酸的pH稳态, 促进细胞的糖酵解过程和恶性行为[48]。

2.3　代谢产物　细胞代谢从静态转变为代谢高度活化状态, 代谢产生的大量产物 (乳酸、核苷酸、氨基酸等) 可作为信号分子调节微环境中的炎症反应, 还可被细胞回收, 促进疾病恶性发展。

乳酸是有氧糖酵解的副产物, 它还可以作为一种信号分子介导细胞的存活与增殖、能量代谢、免疫调节等。乳酸能够作为炎症信号分子, 驱动T细胞功能障碍和增加炎症细胞因子产生, 促进慢性炎症[49]。乳酸在肿瘤细胞中存在穿梭现象, 即通过MCT在不同细胞间交换乳酸, 乳酸穿梭是肿瘤细胞糖代谢重编程的核心影响因素。乳酸还能通过乳酸化修饰这一蛋白翻译后修饰作用, 影响调节性T细胞的稳定性和功能, 促使TAMs转向M2促瘤表型[50,51]。在RA炎症关节中, 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, 加重病情[52]。

2.4　其他关键信号分子　HIF-1α是糖代谢重编程的调节剂和多个信号通路的枢纽, 其作为上游靶点激活一系列通路影响有氧糖酵解过程, 还可直接增加糖酵解关键酶的表达, 促进细胞糖酵解[53]。另外, HIF-1α是肿瘤耐药性的靶点, 其通过诱导肿瘤细胞糖代谢重编程, 降低治疗药物的敏感性[54]。在RA中, HIF-1α通过增加GLUTs表达, 诱导FLSs转向促炎表型[46]。也有研究发现, AD在小胶质细胞激活期间, 细胞发生的糖代谢重编程依赖于HIF-1α通路的调节[21]。

ROS是一种由O_2通过胞内生理活动产生的化学反应自由基, 维持其水平的平衡对细胞生存至关重要。在炎性微环境下, 高度表达的ROS会因其毒性抑制细胞生长[55]。同时, 高水平的ROS会启动氧化应激, 激

活自噬。自噬作为一种重要的细胞修复机制, 对肿瘤抑制/促进取决于疾病状态, 如在肿瘤维持和转移阶段自噬通常作为驱动力[56]。

3 靶向有氧糖酵解过程中关键信号分子的化合物或药物

在炎症相关疾病中, 有氧糖酵解为异常增殖细胞和失调的免疫反应提供能量和大分子合成材料。因此, 靶向有氧糖酵解过程中的关键信号分子控制有氧糖酵解, 相比于全局糖酵解抑制是一种更安全和更具吸引力的治疗策略。靶向治疗的化合物或药物发挥作用的机制多数为直接或间接作用于有氧糖酵解过程的关键蛋白, 进而抑制细胞有氧糖酵解和ATP的产生, 最终导致细胞凋亡。

早在1950年, 针对肿瘤中糖酵解的治疗方案已被提出; 近年来, 糖酵解抑制剂逐渐被发现与开发, 部分抑制剂已经处于临床前和临床试验阶段[57]。3-BrPA作为传统的HK2抑制剂, 对肿瘤组织具有特异性毒性。3-BrPA通过诱导线粒体功能障碍, 促使肿瘤细胞凋亡[58]。HK2另一抑制剂—氯尼达明在临床上已用于多种肿瘤的治疗, 其可阻断糖酵解和PPP途径, 但缺点是作用可逆且时间短。随着研究不断深入, 氯尼达明被发现对MCT1和MCT4的功能也具有抑制作用[59,60]。PFKFB3特异性抑制剂—3PO和PFK15通过抑制炎症相关疾病中病理性微血管的新生, 发挥抗炎作用, 从而减轻疾病恶化程度[61,62]。紫草素是目前发现的PKM2最有效的选择性抑制剂之一, 可剂量依赖性致使肿瘤细胞凋亡, 与其他抗肿瘤药物联用能够提高药物的敏感性, 发挥协同抗肿瘤作用。在RA中, 紫草素通过干扰巨噬细胞的活化, 减少炎症因子释放[63,64]。FX11通过特异性抑制LDHA, 诱导细胞周期阻滞和凋亡, 已在多种肿瘤治疗中显示出临床前疗效, 但使用高浓度的FX11可能会出现脱靶效应[65]。PDK1抑制剂二氯乙酸已经进入II期临床试验阶段, 然而, 二氯乙酸的弱抗癌活性和神经毒性等导致其在临床应用具有一定的局限性[66]。

目前, 靶向有氧糖酵解过程中关键信号分子的化合物或药物如表1总结所示。

4 总结与展望

糖代谢重编程参与炎症相关疾病的发生发展, 在炎性微环境下细胞优先选择有氧糖酵解为快速生长提供能量和营养物质, 维持细胞异常增殖, 导致疾病恶化[67]。炎症相关疾病的糖代谢重编程由STAT3/c-Myc、NF-κB和HIF-1α等多条信号通路单独或协同调控。近年来研究发现, 这些通路具有控制葡萄糖代谢和免疫的双重功能, 即它们能够同时对免疫异常做出应答, 并参与机体炎性微环境的塑造。深入探索相关信号通路在炎症相关疾病中的作用机制有助于阐明糖代谢重编程与炎症相关疾病之间的联系, 并激发新的疾病治疗策略的引入。此外, 靶向有氧糖酵解过程关键信号分子的化合物研发也极具吸引力, 有可能为炎症相关疾病治疗提供新策略。大多数已有报道的糖酵解抑制剂处于临床前研究阶段, 且目前单一的糖酵解抑制剂存在生物利用度低、特异性差等缺点, 但其与临床治疗药物或多种抑制剂的联用可能为疾病的治疗提供新方向[57]。因此, 未来继续深入探讨有氧糖酵解对炎症相关疾病发生和发展的影响及机制, 有助于发现该途径中的新靶点, 为疾病的治疗提供更多理论依据。

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Table 1 Compounds or drugs that target key signalling molecules in aerobic glycolysis. DCA: Dichloroacetic acid; OXPHOS: Oxidative phosphorylation

Compound/drug	Mechanism of action	Clinical stage	Indication	Shortcoming
HK2 inhibitor				
Lonidamine	Inhibited HK2 and blocked aerobic glycolysis and PPP	Marketed	Breast cancer	Weak therapeutic effect when used alone; short duration of action and reversible
3-BrPA	Induced mitochondrial dysfunction and tumor cell apoptosis	Pre-clinical	Liver cancer	Short half-life; chemically unstable
PFKFB3 inhibitor				
3PO	Inhibited aerobic glycolysis and inhibited pathological microvascular neogenesis	Pre-clinical	Breast cancer; RA	Poor water solubility; poor specificity
PFK15		Pre-clinical	Gastric cancer	Poor specificity
PKM2 inhibitor				
Shikonin	Inhibited pyruvate kinase activity and nuclear translocation of PKM2; interfered with macrophage activation	Pre-clinical	Liver cancer; RA	Poor bioavailability; poor specificity
LDHA inhibitor				
FX11	Induced cell cycle arrest and apoptosis	Pre-clinical	Liver cancer	Off-target effect
PDK1 inhibitor				
DCA	Inhibited of PDK1 and shifted metabolism to OXPHOS	Phase II	Glioblastoma	Neurotoxicity

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References

[1] Qin C, Yang G, Yang J, et al. Metabolism of pancreatic cancer: paving the way to better anticancer strategies [J]. Mol Cancer, 2020, 19: 50.

[2] McGarry T, Biniecka M, Veale DJ, et al. Hypoxia, oxidative stress and inflammation [J]. Free Radic Biol Med, 2018, 125: 15-24.

[3] Warburg O. On respiratory impairment in cancer cells [J]. Science, 1956, 124: 269-270.

[4] Jacquier V, Gitenay D, Cavaillès V, et al. The transcription coregulator RIP140 inhibits cancer cell proliferation by targeting the pentose phosphate pathway [J]. Int J Mol Sci, 2022, 23: 7419.

[5] Zhang S, Li J, Xie P, et al. STAT3/c-Myc axis-mediated metabolism alternations of inflammation-related glycolysis involve with colorectal carcinogenesis [J]. Rejuvenation Res, 2019, 22: 138-145.

[6] Zhang X, Li Y, Ma Y, et al. Yes-associated protein (YAP) binds to HIF-1α and sustains HIF-1α protein stability to promote hepatocellular carcinoma cell glycolysis under hypoxic stress [J]. J Exp Clin Cancer Res, 2018, 37: 216.

[7] Ma S, Sun B, Duan S, et al. YTHDF2 orchestrates tumor-associated macrophage reprogramming and controls antitumor immunity through $CD8^+$ T cells [J]. Nat Immunol, 2023, 24: 255-266.

[8] Wu F, Wang S, Zeng Q, et al. TGF-βRII regulates glucose metabolism in oral cancer-associated fibroblasts *via* promoting PKM2 nuclear translocation [J]. Cell Death Discov, 2022, 8: 3.

[9] Jiang Y, Han Q, Zhao H, et al. Promotion of epithelial-mesenchymal transformation by hepatocellular carcinoma-educated macrophages through Wnt2b/β-catenin/c-Myc signaling and reprogramming glycolysis [J]. J Exp Clin Cancer Res, 2021, 40: 13.

[10] Jiang S, Feng R, Tian Z, et al. Metabolic dialogs between B cells and the tumor microenvironment: implications for anticancer immunity [J]. Cancer Lett, 2023, 556: 216076.

[11] Canavan M, Marzaioli V, McGarry T, et al. Rheumatoid arthritis synovial microenvironment induces metabolic and functional adaptations in dendritic cells [J]. Clin Exp Immunol, 2020, 202: 226-238.

[12] Bustamante MF, Oliveira PG, Garcia-Carbonell R, et al. Hexokinase 2 as a novel selective metabolic target for rheumatoid arthritis [J]. Ann Rheum Dis, 2018, 77: 1636-1643.

[13] McGarry T, Orr C, Wade S, et al. JAK/STAT blockade alters synovial bioenergetics, mitochondrial function, and proinflammatory mediators in rheumatoid arthritis [J]. Arthritis Rheumatol, 2018, 70: 1959-1970.

[14] Wang Y, Bao X, Xian H, et al. Glucocorticoid receptors involved in ginsenoside compound K ameliorate adjuvant arthritis by inhibiting the glycolysis of fibroblast-like synoviocytes *via* the NF-κB/HIF-1α pathway [J]. Pharm Biol, 2023, 61: 1162-1174.

[15] Cai W, Cheng J, Zong S, et al. The glycolysis inhibitor 2-deoxyglucose ameliorates adjuvant-induced arthritis by regulating macrophage polarization in an AMPK-dependent manner [J]. Mol Immunol, 2021, 140: 186-195.

[16] Garcia-Carbonell R, Divakaruni AS, Lodi A, et al. Critical role of glucose metabolism in rheumatoid arthritis fibroblast-like synoviocytes [J]. Arthritis Rheumatol, 2016, 68: 1614-1626.

[17] Saeki N, Imai Y. Reprogramming of synovial macrophage metabolism by synovial fibroblasts under inflammatory conditions [J]. Cell Commun Signal, 2020, 18: 188.

[18] Weyand CM, Goronzy JJ. Immunometabolism in the development of rheumatoid arthritis [J]. Immunol Rev, 2020, 294: 177-187.

[19] Ma X, Zhang Y, Gou D, et al. Metabolic reprogramming of microglia enhances proinflammatory cytokine release through EphA2/p38 MAPK pathway in Alzheimer's disease [J]. J Alzheimers Dis, 2022, 88: 771-785.

[20] Fairley LH, Lai KO, Wong JH, et al. Mitochondrial control of microglial phagocytosis by the translocator protein and hexokinase 2 in Alzheimer's disease [J]. Proc Natl Acad Sci U S A, 2023, 120: e2209177120.

[21] Baik SH, Kang S, Lee W, et al. A breakdown in metabolic reprogramming causes microglia dysfunction in Alzheimer's disease [J]. Cell Metab, 2019, 30: 493-507.

[22] Andersen JV, Skotte NH, Christensen SK, et al. Hippocampal disruptions of synaptic and astrocyte metabolism are primary events of early amyloid pathology in the 5×FAD mouse model of Alzheimer's disease [J]. Cell Death Dis, 2021, 12: 954.

[23] Zyśk M, Beretta C, Naia L, et al. Amyloid-β accumulation in human astrocytes induces mitochondrial disruption and changed energy metabolism [J]. J Neuroinflammation, 2023, 20: 43.

[24] Liao HJ, Chu CL, Wang SC, et al. Increased HIF-1α expression in T cells and associated with enhanced Th17 pathway in systemic lupus erythematosus [J]. J Formos Med Assoc, 2022, 121: 2446-2456.

[25] Wang XY, Wei Y, Hu B, et al. C-Myc-driven glycolysis polarizes functional regulatory B cells that trigger pathogenic inflammatory responses [J]. Signal Transduct Target Ther, 2022, 7: 105.

[26] Jia Y, Chen J, Zheng Z, et al. Tubular epithelial cell-derived extracellular vesicles induce macrophage glycolysis by stabilizing HIF-1α in diabetic kidney disease [J]. Mol Med, 2022, 28: 95.

[27] Chen L, Lin X, Lei Y, et al. Aerobic glycolysis enhances HBx-initiated hepatocellular carcinogenesis *via* NF-κB p65/HK2 signalling [J]. J Exp Clin Cancer Res, 2022, 41: 329.

[28] Xian H, Wang Y, Bao X, et al. Hexokinase inhibitor 2-deoxyglucose coordinates citrullination of vimentin and apoptosis of fibroblast-like synoviocytes by inhibiting HK2/

mTORC1-induced autophagy [J]. Int Immunopharmacol, 2023, 114: 109556.

[29] Leng L, Yuan Z, Pan R, et al. Microglial hexokinase 2 deficiency increases ATP generation through lipid metabolism leading to *β*-amyloid clearance [J]. Nat Metab, 2022, 4: 1287-1305.

[30] Yu H, Dai C, Zhu W, et al. PFKFB3 increases IL-1*β* and TNF-*α* in intestinal epithelial cells to promote tumorigenesis in colitis-associated colorectal cancer [J]. J Oncol, 2022, 2022: 6367437.

[31] Long Q, Zou X, Song Y, et al. PFKFB3/HIF-1*α* feedback loop modulates sorafenib resistance in hepatocellular carcinoma cells [J]. Biochem Biophys Res Commun, 2019, 513: 642-650.

[32] Fu W, Shi D, Westaway D, et al. Bioenergetic mechanisms in astrocytes may contribute to amyloid plaque deposition and toxicity [J]. J Biol Chem, 2015, 290: 12504-12513.

[33] Yang JG, Wang WM, Xia HF, et al. Lymphotoxin-*α* promotes tumor angiogenesis in HNSCC by modulating glycolysis in a PFKFB3-dependent manner [J]. Int J Cancer, 2019, 145: 1358-1370.

[34] Angiari S, Runtsch MC, Sutton CE, et al. Pharmacological activation of pyruvate kinase M2 inhibits $CD4^+$ T cell pathogenicity and suppresses autoimmunity [J]. Cell Metab, 2020, 31: 391-405.

[35] Gao S, Chen M, Wei W, et al. Crosstalk of mTOR/PKM2 and STAT3/c-Myc signaling pathways regulate the energy metabolism and acidic microenvironment of gastric cancer [J]. J Cell Biochem, 2019, 120: 1193-1202.

[36] Shirai T, Nazarewicz RR, Wallis BB, et al. The glycolytic enzyme PKM2 bridges metabolic and inflammatory dysfunction in coronary artery disease [J]. J Exp Med, 2016, 213: 337-354.

[37] Damasceno LEA, Prado DS, Veras FP, et al. PKM2 promotes Th17 cell differentiation and autoimmune inflammation by fine-tuning STAT3 activation [J]. J Exp Med, 2020, 217: e20190613.

[38] Yang Q, Wu F, Zhang Y, et al. FOXM1 regulates glycolysis in nasopharyngeal carcinoma cells through PDK1 [J]. J Cell Mol Med, 2022, 26: 3783-3796.

[39] De RV, Iommelli F, Terlizzi C, et al. Non-canonical role of PDK1 as a negative regulator of apoptosis through macromolecular complexes assembly at the ER-mitochondria interface in oncogene-driven NSCLC [J]. Cancers (Basel), 2021, 13: 4133.

[40] Zhou M, He J, Li Y, et al. N^6-methyladenosine modification of REG1*α* facilitates colorectal cancer progression *via* *β*-catenin/Myc/LDHA axis mediated glycolytic reprogramming [J]. Cell Death Dis, 2023, 14: 557.

[41] Shi L, Duan R, Sun Z, et al. LncRNA GLTC targets LDHA for succinylation and enzymatic activity to promote progression and radioiodine resistance in papillary thyroid cancer [J]. Cell Death Differ, 2023, 30: 1517-1532.

[42] Souto-Carneiro MM, Klika KD, Abreu MT, et al. Effect of increased lactate dehydrogenase A activity and aerobic glycolysis on the proinflammatory profile of autoimmune $CD8^+$ T cells in rheumatoid arthritis [J]. Arthritis Rheumatol, 2020, 72: 2050-2064.

[43] Liu X, Yang Z, Chen Z, et al. Effects of the suppression of lactate dehydrogenase A on the growth and invasion of human gastric cancer cells [J]. Oncol Rep, 2015, 33: 157-162.

[44] Li F, He C, Yao H, et al. GLUT1 regulates the tumor immune microenvironment and promotes tumor metastasis in pancreatic adenocarcinoma *via* ncRNA-mediated network [J]. J Cancer, 2022, 13: 2540-2558.

[45] Li B, Kang H, Xiao Y, et al. LncRNA GAL promotes colorectal cancer liver metastasis through stabilizing GLUT1 [J]. Oncogene, 2022, 41: 1882-1894.

[46] Koedderitzsch K, Zezina E, Li L, et al. TNF induces glycolytic shift in fibroblast like synoviocytes *via* GLUT1 and HIF1*α* [J]. Sci Rep, 2021, 11: 19385.

[47] Zhang G, Zhang Y, Dong D, et al. MCT1 regulates aggressive and metabolic phenotypes in bladder cancer [J]. J Cancer, 2018, 9: 2492-2501.

[48] Sheng G, Gao Y, Wu H, et al. Functional heterogeneity of MCT1 and MCT4 in metabolic reprogramming affects osteosarcoma growth and metastasis [J]. J Orthop Surg Res, 2023, 18: 131.

[49] Song C, Wang S, Fu Z, et al. IGFBP5 promotes diabetic kidney disease progression by enhancing PFKFB3-mediated endothelial glycolysis [J]. Cell Death Dis, 2022, 13: 340.

[50] Gu J, Zhou J, Chen Q, et al. Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF-*β* signaling in regulatory T cells [J]. Cell Rep, 2022, 39: 110986.

[51] Ge WX, Yan SJ, Wan GH. The immunomodulatory effect of lactic acid within the tumor microenvironment [J]. Acta Pharm Sin (药学学报), 2022, 57: 2570-2579.

[52] Pucino V, Certo M, Bulusu V, et al. Lactate buildup at the site of chronic inflammation promotes disease by inducing $CD4^+$ T cell metabolic rewiring [J]. Cell Metab, 2019, 30: 1055-1074.

[53] Chen X, Luo C, Bai Y, et al. Analysis of hypoxia inducible factor-1*α* expression and its effects on glycolysis of esophageal carcinoma [J]. Crit Rev Eukaryot Gene Expr, 2022, 32: 47-66.

[54] Dong S, Liang S, Cheng Z, et al. ROS/PI3K/Akt and Wnt/*β*-catenin signalings activate HIF-1*α*-induced metabolic reprogramming to impart 5-fluorouracil resistance in colorectal cancer [J]. J Exp Clin Cancer Res, 2022, 41: 15.

[55] Jin Y, Huynh DTN, Heo KS. Ginsenoside Rh1 inhibits tumor growth in MDA-MB-231 breast cancer cells *via* mitochondrial ROS and ER stress-mediated signaling pathway [J]. Arch Pharm Res, 2022, 45: 174-184.

[56] Yang C, Yaolin S, Lu W, et al. G-protein signaling modulator 1 promotes colorectal cancer metastasis by PI3K/AKT/mTOR signaling and autophagy [J]. Int J Biochem Cell Biol, 2023, 157: 106388.

[57] Ganapathy-Kanniappan S, Geschwind JF. Tumor glycolysis as a target for cancer therapy: progress and prospects [J]. Mol

Cancer, 2013, 12: 152.

[58] Zou X, Zhang M, Sun Y, et al. Inhibitory effects of 3-bromopyruvate in human nasopharyngeal carcinoma cells [J]. Oncol Rep, 2015, 34: 1895-1904.

[59] Huang Y, Sun G, Sun X, et al. The ptential of lonidamine in combination with chemotherapy and physical therapy in cancer treatment [J]. Cancers (Basel), 2020, 12: 3332.

[60] Nancolas B, Guo L, Zhou R, et al. The anti-tumour agent lonidamine is a potent inhibitor of the mitochondrial pyruvate carrier and plasma membrane monocarboxylate transporters [J]. Biochem J, 2016, 473: 929-936.

[61] Biniecka M, Canavan M, McGarry T, et al. Dysregulated bioenergetics: a key regulator of joint inflammation [J]. Ann Rheum Dis, 2016, 75: 2192-2200.

[62] Matsumoto K, Noda T, Kobayashi S, et al. Inhibition of glycolytic activator PFKFB3 suppresses tumor growth and induces tumor vessel normalization in hepatocellular carcinoma [J]. Cancer Lett, 2021, 500: 29-40.

[63] Liu T, Li S, Wu L, et al. Experimental study of hepatocellular carcinoma treatment by shikonin through regulating PKM2 [J]. J Hepatocell Carcinoma, 2020, 7: 19-31.

[64] Xu J, Jiang C, Wang X, et al. Upregulated PKM2 in macrophages exacerbates experimental arthritis *via* STAT1 signaling [J]. J Immunol, 2020, 205: 181-192.

[65] Rellinger EJ, Craig BT, Alvarez AL, et al. FX11 inhibits aerobic glycolysis and growth of neuroblastoma cells [J]. Surgery, 2017, 161: 747-752.

[66] Carbone D, de Franco M, Pecoraro C, et al. Discovery of the 3-amino-1, 2, 4-triazine-based library as selective PDK1 inhibitors with therapeutic potential in highly aggressive pancreatic ductal adenocarcinoma [J]. Int J Mol Sci, 2023, 24: 3679.

[67] Ganapathy-Kanniappan S. Molecular intricacies of aerobic glycolysis in cancer: current insights into the classic metabolic phenotype [J]. Crit Rev Biochem Mol Biol, 2018, 53: 667-682.