基于有氧糖酵解调节的纳米药物递送系统用于肿瘤治疗的研究进展

李一菁[1], 黄胜楠[2,3*], 王子昂[1], 直炜炜[1], 祝侠丽[1*]

(1. 河南中医药大学药学院, 河南 郑州 450046; 2. 河南中医药大学中医药科学院, 河南 郑州 450046;
3. 河南中医药大学豫药全产业链研发河南省协同创新中心, 河南 郑州 450046)

摘要: 肿瘤是严重威胁人类健康的难题之一。常用的肿瘤治疗手段均存在一定的局限性, 治疗效果不佳, 亟待开发新的抗肿瘤策略。在有氧条件下, 肿瘤细胞利用糖酵解产生能量的过程称为有氧糖酵解。有氧糖酵解与肿瘤生长、增殖和转移联系密切, 为肿瘤治疗提供了新的靶点。纳米药物递送系统因具有可靶向给药、提高疗效和降低毒副作用等优势, 被广泛用于靶向肿瘤治疗研究。大量研究表明, 越来越多的纳米药物递送系统可通过靶向肿瘤有氧糖酵解过程的信号因子、反应产物等潜在靶点调节有氧糖酵解代谢, 进而提升抗肿瘤作用。本文综述了纳米药物递送系统在调节肿瘤有氧糖酵解中的应用, 为实现肿瘤的高效靶向治疗提供理论参考。

关键词: 有氧糖酵解; 纳米药物递送系统; 肿瘤治疗; 联合治疗

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2024)09-2509-10

Research progress of nanomedical drug delivery system based on aerobic glycolytic regulation for tumor therapy

LI Yi-jing[1], HUANG Sheng-nan[2,3*], WANG Zi-ang[1], ZHI Wei-wei[1], ZHU Xia-li[1*]

(*1. Pharmacy College, Henan University of Chinese Medicine, Zhengzhou 450046, China; 2. Academy of Chinese Medical Sciences, Henan University of Chinese Medicine, Zhengzhou 450046, China; 3. Collaborative Innovation Center of Research and Development on the Whole Industry Chain of Yu-Yao Henan Province, Henan University of Chinese Medicine, Zhengzhou 450046, China*)

Abstract: Tumor is one of the serious problems threatening human health. There are some limitations in the delivery of commonly used tumor therapy technologies, and the therapeutic effect is not satisfactory, so new anti-tumor strategies need to be developed. The process of tumor cells using glycolysis to produce energy under aerobic conditions is called aerobic glycolysis, which is closely related to tumor growth, proliferation and metastasis, and can provide a new target spot for tumor treatment. Nano drug delivery system has been widely used in targeted tumor therapy because of its advantages of targeted drug delivery, improved anti-tumor efficacy and reduced toxic side effects. Numerous studies have shown that more and more nano drug delivery systems regulates aerobic glycolytic metabolism by targeting to potential targets such as signaling factors or reaction products of aerobic glycolytic process in tumors, and therefore enhance the anti-tumor effect. This paper reviews the application of nano drug delivery system in regulating tumor aerobic glycolysis, and provides theoretical references for realizing efficient targeted tumor therapy.

Key words: aerobic glycolysis; nano drug delivery system; tumor therapy; combined therapy

收稿日期: 2024-01-22; 修回日期: 2024-06-11.

基金项目: 国家自然科学基金资助项目 (82003298); 河南省科技攻关项目 (232102310392); 河南省博士后科研项目 (201901025); 河南省肿瘤重大疾病靶向治疗与诊断重点实验室开放基金 (NMZL2020102); 河南省高等学校重点科研项目 (23A360007).

*通讯作者 Tel: 18790299362, E-mail: huangsn2019@hactcm.edu.cn;
Tel: 13783470772, E-mail: zhuxiali1980@126.com

DOI: 10.16438/j.0513-4870.2024-0068

肿瘤作为困扰人类健康的一大难题, 因其全身性、多病因的复杂性而受到广泛研究[1,2]。目前临床肿瘤治疗方法主要为外科手术、化学疗法和放射疗法[3], 其中外科手术只适合于部分实体瘤的切除, 化疗药物存在水溶性差、易产生耐药性、缺乏靶向性等缺点, 放疗具有较强的毒副作用[4]。因此, 亟待开发新的安全、高效的肿瘤治疗方法。20世纪20年代, 德国著名科学家Otto Warburg提出了Warburg效应: 即使在有氧条件下, 肿瘤细胞也通过糖酵解途径将葡萄糖转化为乳酸[5]。与正常细胞相比, 肿瘤细胞更容易出现“葡萄糖饥饿”现象[6], 主要表现为葡萄糖摄取率增加和糖代谢产物乳酸含量较高。由于肿瘤细胞的增殖具有高度的有氧糖酵解依赖性[7], 因此调节肿瘤细胞有氧糖酵解是一种非常有前景的治疗策略。近年来, 随着纳米技术的深入研究, 纳米药物递送系统 (nano drug delivery system, NDDS) 因具有高效载药、靶向给药[8]和渗透与滞留增强效应 (enhanced permeability and retention effect, EPR effect) 等优势逐渐被发现并应用于基于糖酵解调节的肿瘤治疗中[9,10]。本文综述了近年来基于糖酵解调节的纳米药物递送系统用于肿瘤治疗研究进展, 并对该领域的发展前景进行了展望。

1 糖酵解的作用机制及潜在靶点

在大多数健康细胞中, 糖酵解反应所生成的还原型辅酶I (nicotinamide adenine dinucleotide, NADH) 和H^+穿梭进入线粒体参与三羧酸循环 (tricarboxylic acid, TCA) 和氧化磷酸化 (oxidative phosphorylation, OXPHOS) 并产生大量腺苷三磷酸 (adenosine triphosphate, ATP)[11], 在缺氧条件下才会由乳酸脱氢酶 (lactate dehydrogenase, LDH) 催化产生乳酸和少量ATP。正常细胞和肿瘤细胞的产能方式对比如图1所示, Warburg效应表明, 有氧糖酵解是大多数肿瘤细胞的显著特征[12]。与TCA循环和OXPHOS相比, 肿瘤细胞更倾向于有氧糖酵解的原因如下: ① 消耗相同葡萄糖分子时, 有氧糖酵解产能效率虽然低, 但是它的产能速度比OXPHOS快100多倍[13]; ② 肿瘤细胞的缺氧环境是支持糖酵解和阻断OXPHOS的关键因素[14]; ③ 糖酵解过程中产生的代谢中间体可以作为合成氨基酸、核苷酸、脂肪酸和糖原等多种代谢途径的前体, 为机体提供一定的物质和能量基础。

有氧糖酵解作为肿瘤细胞代谢的支柱, 充分满足肿瘤细胞快速增长所需要的能量和原料代谢需求[15,16], 与肿瘤细胞内缺氧的微环境具有协同作用, 促进肿瘤的增殖、侵袭和转移, 并通过多种途径抑制肿瘤免疫[17]。由于肿瘤细胞的增殖与有氧糖酵解密切相关[18], 因此有氧糖酵解所涉及的信号因子、反应产物、

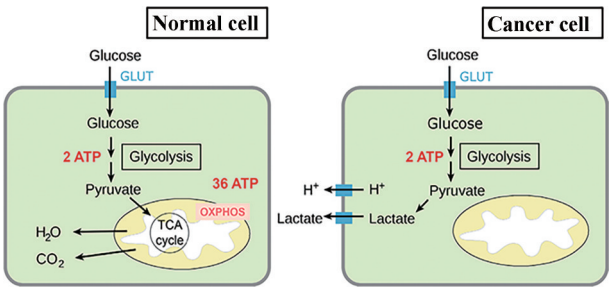

Figure 1 The main pathways of energy production from glucose in normal and cancer cells[12]. Adapted from Ref. 12 with permission. Copyright © 2023 Uspekhi Biologicheskoi Khimii

信号通路及关键酶等均可以作为肿瘤治疗的潜在靶点。下文针对信号因子、反应产物和关键酶对有氧糖酵解的作用机制进行简要阐述。

1.1 信号因子 缺氧诱导因子-1 (hypoxia-inducible factor-1, HIF-1) 是协调响应低氧环境而触发的细胞适应性机制, 在肿瘤快速生长过程中对活性氧 (reactive oxygen species, ROS) 敏感, 是发生在缺氧肿瘤细胞中代谢重编程的关键调节剂[19]。研究证实, HIF-1通过上调葡萄糖转运蛋白 (glucose transporter, GLUT) 的表达和增强糖酵解途径中关键酶, 包括己糖激酶2 (hexokinase 2, HK2)、丙酮酸脱氢酶激酶 (pyruvate dehydrogenase kinase, PDK)、磷酸果糖激酶1 (phosphofructokinase 1, PFK1)、丙酮酸激酶M2 (pyruvate kinase M2, PKM2) 和LDH的转录而提高葡萄糖摄取, 增加糖酵解速度, 而这些糖酵解关键酶反过来又维持着HIF-1活性[20], 从而不断提供肿瘤细胞所需的能量; 其次, HIF-1还可以通过多种机制影响多种线粒体活动, 包括线粒体氧化能力、凋亡、分裂和自噬, 从而导致线粒体功能障碍[21], 促进肿瘤细胞有氧糖酵解的进行; 此外, 在缺氧条件下, HIF-1可以调节PI3K/Akt信号通路[22], 促进血管生成因子的转录, 增强肿瘤细胞的侵袭和转移能力[23,24]。

除主调节因子HIF-1外, 越来越多的调节因子被证实能够驱动肿瘤细胞的糖酵解。研究表明, 长链非编码RNA (long non coding RNA, lncRNA) 在肿瘤糖酵解中也发挥着重要作用, Zhang等[25]发现lncRNA-MIF能够通过抑制c-Myc和miR-586而抑制有氧糖酵解和肿瘤发生; 此外, Pate等[26]证明Wnt信号通路通过介导的PDK1表达可以促进糖酵解和肿瘤生长。

1.2 反应产物 乳酸 (lactic acid, LA) 作为有氧糖酵解的最终产物, 在肿瘤细胞生长增殖、免疫治疗等方面均发挥着重要作用[27]。首先, 乳酸作为供能物质和信号因子, 为肿瘤细胞生长提供充分的能量和转移条件。Yang等[28]通过转录组学技术分析了乳酸对小鼠巨噬细

胞转录水平的影响, 结果表明乳酸能够激活PI3K-Akt通路, 上调肿瘤血管内皮生长因子 (vascular endothelial growth factor, VEGF) 的产生, 促进肿瘤细胞血管生成, 进而驱动肿瘤细胞生长和增殖。此外, 乳酸作为代谢产物被转运至细胞外, 大量的乳酸堆积形成了过酸性的肿瘤微环境, 增强了肿瘤细胞迁移能力和抗凋亡能力[18,29]。Brand等[30]证明过酸性的肿瘤微环境中自然杀伤细胞 (natural killer, NK) 数量较少且其细胞活性较低, 乳酸的分泌保护肿瘤干细胞免受NK细胞的攻击, 进一步促进了肿瘤细胞转移; Apicella等[31]发现肿瘤细胞中分泌的大量乳酸不仅能促进肿瘤转移, 并且是肿瘤抵抗药物治疗的关键调控分子。与此同时, 乳酸的大量生成使得肿瘤细胞对免疫治疗产生一定的抵抗作用。Kumagai等[32]证明乳酸促进高度糖酵解肿瘤微环境中调节性T细胞的蛋白质程序性细胞死亡配体1 (protein programmed cell death ligand 1, PD-L1) 表达, 而抑制$CD8^+$ T细胞PD-L1表达, 导致PD-1阻断疗法失效。Wang等[33]发现糖酵解产生的乳酸可以抑制M1巨噬细胞标志物在RNA和蛋白质水平的表达, 进而抑制M1巨噬细胞的抗肿瘤作用。

1.3 关键酶 糖酵解主要由催化葡萄糖转化为葡萄糖-6磷酸的HK2、催化葡萄糖6-磷酸转化为果糖6-磷酸的PFK1、催化磷酸烯醇式丙酮酸转化为丙酮酸和ATP的PKM2和催化丙酮酸转化为乳酸的LDH等关键酶所介导, 这些关键酶是肿瘤发生、侵袭和转移的重要参与者[34]。研究表明, 有氧糖酵解中的关键酶可以促进内皮细胞迁移和血管内皮生长因子分泌, 介导肿瘤血管生成[35]。Xia等[36]证明在膀胱癌细胞质中, 过度表达的PKM2会与STAT3结合形成复合物, 转入细胞核激活HIF-1α和VEGF, 进而促进肿瘤血管生成。此外, 糖酵解关键酶可以通过调节PD-L1的表达或调节免疫细胞激活和浸润, 介导肿瘤免疫逃逸[34]。Serganova等[37]证明LDHA可以通过上调HIF-1α信号通路并抑制肿瘤微环境 (tumor microenvironment, TME) 中$CD3^+$ T细胞和$CD4^+$ T细胞浸润来促进肿瘤转移。除上述作用机制外, 一些有氧糖酵解关键酶在肿瘤相关成纤维细胞 (cancer-associated fibroblasts, CAF) 的致癌作用中也发挥着重要作用。Zhang等[38]在非小细胞肺癌 (non-small cell lung cancer, NSCLC) 中发现, CAFs能够上调和稳定c-Myc, 通过激活NSCLC细胞的Wnt/β-catenin通路导致糖酵解关键酶HK2激酶的转录激活, 进而促进肿瘤有氧糖酵解。

2 具有调节有氧糖酵解作用的药物

2.1 中药单体 研究表明, 许多中药单体可以通过靶向有氧糖酵解的信号通路或关键酶发挥抑制肿瘤细胞生长、诱导肿瘤细胞凋亡等作用, 且同一中药有效成分可以在不同肿瘤细胞和不同信号通路中发挥抗肿瘤疗效。例如从豆科植物苦参中提取的天然生物碱–苦参碱既可以抑制HIF-1α的表达而抑制结肠癌细胞的生长[39], 也可以抑制PKM2的活性而阻止结肠癌细胞的转移[40]; 从紫草树根中提取的天然萘醌类化合物–紫草素, 可以在结直肠癌[41]、胃癌[42]及肝癌[43]等不同肿瘤细胞中调控PKM2、c-Myc、HIF-1α等信号通路, 抑制肿瘤细胞的有氧糖酵解, 发挥抗肿瘤作用。具有调节有氧糖酵解功能的中药单体成分见表1[44-62]。

2.2 化学药物 迄今为止, 化学疗法仍是临床抗肿瘤治疗的主要手段, 许多化学药物在抑制肿瘤有氧糖酵解过程中的作用机制也逐渐被发现。Peng等[63]揭示了

Table 1 Traditional Chinese medicine monomers that have the function of regulating aerobic glycolysis

Active components of Chinese medicine	Target spot	Cancer type	Reference
Epigallocatechin gallate	PI2K, Akt	Pancreatic cancer	[44]
Quercetin	Akt/mTOR	Thyroid cancer	[45]
Salidroside	ERK/HIF-1α	Gallbladder cancer	[46]
Kaempferol	JAK2/STAT3	Cervical cancer	[47]
Diosgenin	Hippo-YAP	Lung cancer	[48]
Evodiamine	HIF, VEGFR	Liver cancer	[49]
Ginkgolide B	JAK2/STAT3	Esophageal cancer	[50]
Nuciferine	Akt/mTOR/4EBP1	Intrahepatic cholangiocarcinoma	[51]
Curcumin	NF-κB-Snail/HK3	Lung cancer	[52]
Deoxyelephantopin	PI3K/Akt/mTOR/HIF-1α	Liver cancer	[53]
Onychin	circ_0136666/miR-370	Lung cancer	[54]
Tanshinone II A	PKM2	Cervical cancer	[55]
Oridonin	circ-LRBA	Bladder cancer	[56]
Juglone	Akt/mTOR	Gastric cancer	[57]
Cucurbitacin B	Akt/mTOR	Intrahepatic cholangiocarcinoma	[58]
Erianin	lncRNA LINC01354/miR-515-5p	Prostatic cancer	[59]
Artemisinin	SIRT2	Cervical cancer	[60]
Icaritin	Akt/mTOR	Intrahepatic cholangiocarcinoma	[61]
Withaferin A	circOSBPL10/miR-128-3p	Breast cancer	[62]

多西他赛在发挥抗肿瘤作用时, 以Smad3依赖性方式下调HIF-1α和PFKP的表达, 从而抑制乳酸生成、葡萄糖摄取和肿瘤细胞增殖。Zhang等[64]研究发现1,25-二羟维生素D_3能够显著降低糖酵解相关蛋白GLUT-1、PKM2、HK2的表达, 显著抑制乳腺癌细胞的糖酵解过程, 并且通过线粒体中Cyt途径诱导肿瘤细胞凋亡。Qi等[65]发现异丙酚可能通过拮抗NMDA受体, 降低细胞内Ca^{2+}浓度, 抑制CaMKII和Akt磷酸化, 并下调HIF-1α的表达, 降低体外肿瘤内皮细胞 (tumor endothelial cells, TECs) 的黏附能力, 从而抑制肿瘤转移。Cheng等[66]研究表明2-脱氧葡萄糖 (2-deoxyglucose, 2DG) 能够结合肿瘤细胞表面的GLUT-1, 通过同葡萄糖竞争作用而阻断肿瘤糖酵解, 从而抑制肿瘤生长。Roy等[67]证明糖酵解抑制剂3-溴丙酮酸 (3-bromopyruvate, 3BP) 能够通过破坏HK2和线粒体电压依赖性阴离子通道1蛋白之间的相互作用, 极大地抑制肿瘤细胞ATP的产生, 切断肿瘤细胞生长所需要的能量来源。

3 基于有氧糖酵解的NDDS

近年来, NDDS被广泛开发用于抗肿瘤药物的高效递送, NDDS是指药物与高分子材料形成的粒径在1～1 000 nm的纳米级递药系统[68], 具有缓控释给药、靶向给药、增强抗肿瘤药物的溶解度和稳定性及降低毒副作用等多重优势[69], 根据设计原理不同, 下面对基于糖酵解的NDDS进行简单介绍。

3.1 本身具有糖酵解调节作用 大量研究表明, 许多金属纳米粒本身能够调节有氧糖酵解相关信号因子, 从而抑制肿瘤糖酵解。Sun等[70]所设计的金纳米粒 (Au nanoparticles, AuNPs) 通过c-Myc依赖性方式下调糖酵解过程中关键酶 (GLUT1和HK2) 的表达, 减少了肿瘤细胞对葡萄糖的摄取及ATP和乳酸的生成, 显著抑制了肿瘤细胞的生长。Ruan等[71]研发了一种具有“一石二鸟”作用的CaO_2@mPDA-SH纳米粒, 当CaO_2暴露于过酸性的肿瘤微环境中时, 消耗乳酸并产生氧气, 缺氧的缓解进一步下调了HIF-1α和糖酵解相关酶 (GLUT1和LDHA) 的表达, 从源头减少乳酸产生, 改善缺氧和乳酸高度积累的肿瘤微环境, 此外, 该纳米粒子还能下调血管生成因子VEGF的表达, 抑制肿瘤细胞增殖。Wu等[72]提出了一种基于锌离子干扰策略的肿瘤饥饿疗法, 该课题组以咪唑酸锌金属有机框架ZIF-8为载体, 通过将一个锌激活型的可以裂解GLUT1 mRNA的DNA酶装载到ZIF-8中, 同时用透明质酸 (hyaluronic acid, HA) 包裹, 构建了一个“纳米能量阻断器”, 该纳米能量阻断器不仅展现了对肿瘤部位的优先积累倾向, 而且通过协同“Zn^{2+}干扰”介导的糖酵解抑制和Zn^{2+}激活的肿瘤特异性GLUT1耗竭实现了糖酵解阻断, 有效地抑制了恶性黑色素瘤的生长。

3.2 负载调节糖酵解的药物 中药单体和部分化疗药物固然能起到调节肿瘤有氧糖酵解的作用, 但是如何高效、靶向地将这些有效成分运送至肿瘤部位以发挥其最大抗肿瘤活性, 离不开NDDS这一强有力的药物载体。Wang等[73]将具有抗肿瘤作用的异甘草素 (isoliquiritigenin, ISL) 包封于纳米脂质体 (nanoliposomes, NLs) 中制备了ISL-NLs, 研究表明ISL-NLs通过上调AMPK蛋白和阻断Akt/mTOR通路中c-Myc、HIF-1α的表达, 减少乳酸生产, 显著抑制结直肠癌细胞的增殖和葡萄糖摄取。该课题组[74]还设计了一种负载桦木酸 (betulinic acid, BA) 的纳米脂质体BA-NLs, 通过研究发现BA-NLs能够抑制糖酵解过程中HK2、PFK-1、PKM2和PEP等关键酶的表达, 显著抑制结肠癌细胞的增殖。Chen等[75]以金纳米棒 (gold nanorods, GNR) 为载体, 在其表面修饰了双氯芬酸 (diclofenac, DC) 共价键连接的透明质酸HA-DC, 制备了GNR/HA-DC (图2A), 肿瘤细胞内高表达的透明质酸酶 (HAase) 触发DC释放, 从而下调GLUT的表达, 抑制葡萄糖摄取和ATP生成, 与光热疗法协同增强体内外抗肿瘤疗效。

3.3 负载糖酵解关键酶抑制剂 大量文献表明, 糖酵解关键酶在有氧糖酵解中不可或缺的关键作用为肿瘤的治疗提供了有价值的治疗靶点。Fang等[76]以Cu纳米粒为载体, 将LDHA金属抑制剂与Cu纳米粒通过Mn (II) 配位组装成近红外光响应纳米粒Mn-CuS, 在其表面附上聚乙二醇叶酸修饰的牛血清白蛋白, 制备了靶向肿瘤的Mn-CuS@BSA-FA, 该纳米粒在肿瘤部位聚集后在近红外照射下释放糖酵解抑制剂, 可以降低LDHA的活性并减弱乳酸和丙酮酸之间的转化。此外, 在体外抗肿瘤活性研究中, 该纳米粒能够抑制HepG-1细胞中HIF-1的表达, 减少ATP生成, 降低肝癌细胞的生长增殖所需的能量。Liu等[77]合成了一种由F127包被的药物二聚体形成的纳米前药, 该二聚体通过二硫键连接氯尼达明 (lonidamine, LND) 和NLG919, 该二硫键可被肿瘤微环境内过量的谷胱甘肽裂解以释放两种药物, 研究表明该纳米前药中所负载的LND不仅可以通过抑制HK2的活性而抑制肿瘤细胞的能量代谢, 而且还可以破坏线粒体的结构, 扰乱肿瘤细胞的能量代谢。

3.4 负载葡萄糖氧化酶 葡萄糖氧化酶 (glucose oxidase, GOx) 是一种内源性氧化还原酶, 能够催化葡萄糖和氧气产生H_2O_2和葡萄糖酸, 加速葡萄糖分解代谢, 切断肿瘤细胞的能量供应, 抑制有氧糖酵解[78,79]。Zhang等[80]以可降解的羟基磷石灰纳米棒为载体, 并在

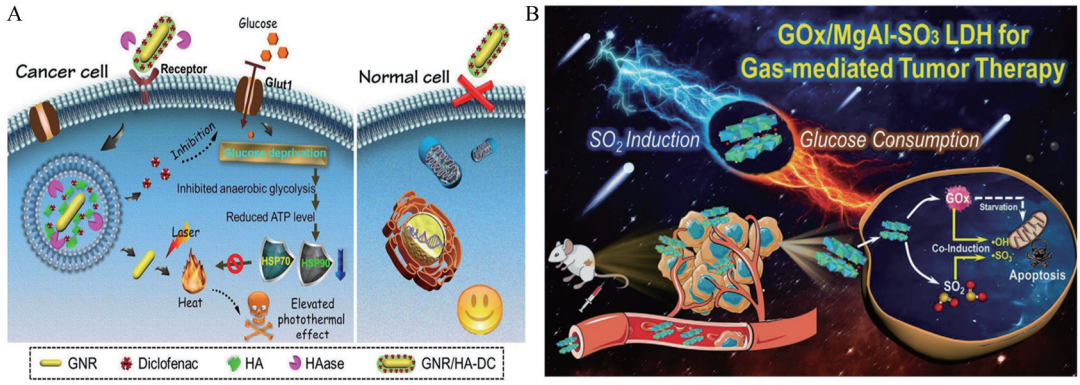

Figure 2 Schematic diagram of the action of NDDS loaded with regulating glycolytic drugs and glucose oxidase. A: Schematic illustration of GNR/HA-DC for selectively sensitizing tumor cells to photothermal therapy by interfering the anaerobic glycolysis metabolism[75]; B: Schematic illustration of GOx/MgAl-SO_3 LDH nanosheets for SO_2-mediated synergistic tumor therapy[82]. NDDS: Nano drug delivery system; HA: Hyaluronic acid; DC: Diclofenac. Adapted from Ref. 75 with permission. Copyright © 2017 American Chemical Society. Adapted from Ref.82 with permission. Copyright © 2021 The Authors

其表面附着GOx、HA和10-羟基喜树碱 (10-hydroxy-camptothecin, CPT), HA的靶向能力使该纳米棒富集在肿瘤部位, 通过释放GOx中断肿瘤细胞有氧糖酵解, 同时促进Ca^{2+}过载和CPT释放, 抑制线粒体和糖酵解产生ATP从而抑制肿瘤能量代谢。Yu等[81]以该课题组先前合成的金纳米粒为载体 (CAuNCs@HA), 在其表明共同吸附GOx和过氧化氢酶 (catalase, CAT), 利用二者之间的级联酶促反应合成了自驱动纳米马达, 与HK-2 siRNA进一步缩合形成最终制剂NM-Si。级联酶促反应可持续产生氧泡, 使纳米粒具有更快的自推进自主运动和更深的肿瘤穿透, 持续产氧的同时下调糖酵解关键酶HK2的表达, 协同缓解缺氧和抑制有氧糖酵解, 重塑TME, 为NDDS高效、精准抗肿瘤提供了新的平台。Chu等[82]合成了由Mg-Al层状双氢氧化物 (MgAl LDH) 组成的精细纳米片 (图2B), 并在其层状结构 (MgAl-SO_3 LDH) 中插入亚硫酸盐, 进一步负载葡萄糖氧化酶得到复合纳米片GOx/MgAl-SO_3 LDH, 呈现出可控的SO_2气体释放和酸性响应, 由于GOx的糖酵解作用, 生成的葡萄糖酸促使细胞内SO_2从纳米片上释放出来, 过量的H_2O_2与SO_2有效反应, 促进有毒自由基的产生, 对肿瘤细胞产生显著的氧化损伤; 此外, GOx/MgAl-SO_3 LDH对细胞内葡萄糖的消耗阻断了肿瘤细胞的能量供应, 有利于体外和体内协同抑制肿瘤。

4 基于有氧糖酵解调节的联合治疗在抗肿瘤中的应用

尽管糖酵解抑制剂在肿瘤治疗中具有潜在的治疗功效, 但是单一的糖酵解抑制剂治疗效果并不理想。因此, 研究者们在抑制肿瘤有氧糖酵解的同时将其应用到与化学疗法、光热疗法、免疫疗法、声动力疗法及饥饿疗法等不同疗法的联合治疗中, 为更好地提高肿瘤治疗效果提供了新的思路。

4.1 与化学疗法的联合治疗 目前, 大量具有糖酵解调节作用的化疗药物为糖酵解联合化疗提供了治疗策略。Zang等[83]构建了一种具有同源靶向能力的仿生纳米系统 (图3A), 将化疗药物紫杉醇和糖酵解抑制剂PFK15共同负载于SLN后, 将其封装在肿瘤细胞和CAF的融合细胞膜中, 同时抑制肿瘤细胞和CAF内的有氧糖酵解, 有效阻断CAF对肿瘤细胞的能量供应, 抑制肿瘤生长并提高紫杉醇的化疗效果。

4.2 与光热疗法的联合治疗 光热疗法 (photothermal therapy, PTT) 是指利用光热剂在光照射下产生大量的热量而杀死肿瘤细胞, 因其选择性高、无创性、耐药性低和不良反应小而被认为是临床和临床前阶段的主要治疗策略之一[84]。Dai等[85]通过制备一种由叶酸修饰的多功能脂质体, 该脂质体负载的2DG通过阻断糖酵解代谢途径抑制ATP和热休克蛋白的生成, 达到了饥饿疗法与PTT协同抗肿瘤的明显效果。Ding等[86]通过将GOx和$CaCO_3$结合到液态金属纳米粒表面, 设计出了一种酸性TME响应型纳米粒 (LMGC), 在肿瘤细胞内释放GOx催化葡萄糖生成葡萄糖酸, 减少了肿瘤细胞对葡萄糖的摄取和能量来源, 与Ca^{2+}干扰线粒体代谢和液态金属纳米粒的光热效应协同作用, 显著抑制了肿瘤细胞的生长。

4.3 与声动力疗法的联合治疗 声动力疗法 (sonodynamic therapy, SDT) 是在光热疗法的基础上衍生出来的非侵入性肿瘤治疗方式, 在外部超声波刺激下, 声敏剂被激活产生ROS并诱导肿瘤细胞凋亡和坏死, 因其具有深层次的渗透力、良好的患者依从性和生物安全性而被广泛开发用于肿瘤治疗[87]。Nguyen Cao等[88]开发了可生物还原的谷胱甘肽 (glutathione, GSH) 响

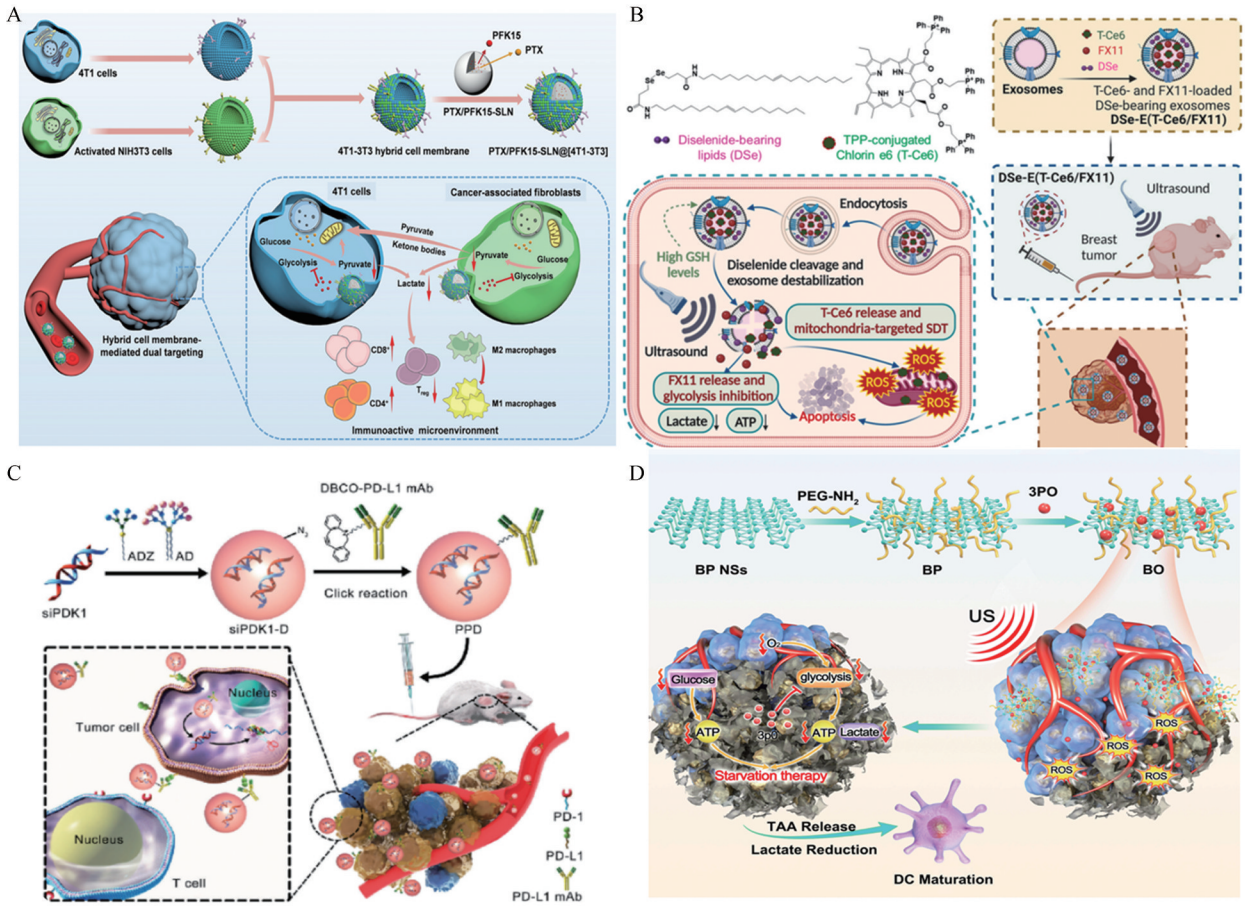

Figure 3 Illustration of glycolytic regulation based NDDS in combination with chemotherapy (A), sonodynamic therapy (B), immunotherapy (C), and multiple therapies (D) for tumor treatment. A: Preparation and therapeutic effect of PTX/PFK15-SLN@[4T1-3T3] NPs[83]; B: Schematic illustration for the preparation of mitochondria-targeting T-Ce6-and FX11-loaded Dse bearing exosomes and their therapeutic actions[88]; C: Schematic illustration of the construction of the PPD, and the targeted delivery to silence PDK1 for anticancer activity[90]; D: Schematic illustration of ultrasound triggered tumor metabolism suppressor induces tumor starvation for enhanced sonodynamic immunotherapy of breast cancer[91].Adapted from Ref.83 with permission. Copyright © 2022 Elsevier; Adapted from Ref.88 with permission. Copyright © 2023 Elsevier; Adapted from Ref.90 with permission. Copyright © 2023 The Authors; Adapted from Ref.91 with permission. Copyright © 2023 Qiao et al

应性二硒化物外泌体 DSe-E (图 3B)，在 TME 中高水平的 GSH 响应下选择性地在肿瘤部位释放所负载的声敏剂二氢卟吩 e6 和糖酵解抑制剂 FX11，在超声波的照射下，三苯基膦修饰的线粒体靶向声敏剂 T-Ce6 产生 ROS 有效破坏肿瘤细胞线粒体并促进细胞凋亡，FX11 减少 ATP 产生，显著抑制细胞能量代谢，为外泌体安全有效地结合 SDT 靶向肿瘤细胞有氧糖酵解提供了新的探索思路。

4.4 与免疫疗法的联合治疗 免疫治疗是一种调节免疫微环境，激活免疫系统的新型疗法，它依赖于自身免疫功能来杀死肿瘤细胞和组织，在产生长期的免疫记忆效应的同时不会对正常组织或细胞造成伤害[89]。Zhang 等[90]建立了一种用 PD-L1 抗体修饰的自组装树突状分子纳米系统 PPD (图 3C)，用于递送靶向 3-磷酸肌醇依赖性蛋白激酶-1 (3-phosphoinositide-dependent protein kinase-1，PDK-1) 的小分子干扰 RNA (small interfering RNA，siRNA)，有效地抑制 PDK-1 诱导的有氧糖酵解和 PD-1/PD-L1 通路相关的免疫反应，在荷瘤小鼠模型中有效地抑制肿瘤生长和转移的同时没有明显的毒性，为自组装树突状分子纳米系统在特异性肿瘤免疫治疗中提供了新的研究思路。

4.5 与多种疗法的联合治疗 随着对有氧糖酵解的深入研究，研究者们逐渐探索出了多种疗法联合抗肿瘤的新策略。Liu 等[77]设计的纳米前药，通过二硫键连接 LND 和 NLG919，该二硫键可与肿瘤微环境内过量的 GSH 反应裂解以释放两种药物，LND 可以降低 HK2 的表达并破坏线粒体以抑制糖酵解的能量供应，NLG919 可以减少犬尿氨酸的积累和调节性 T 细胞的

数量, 从而缓解免疫抑制微环境, 且二硫键对GSH的消耗增加了细胞内氧化应激并引发肿瘤细胞的免疫原性细胞死亡, 该纳米前药的研发为化学疗法联合免疫疗法治疗有氧糖酵解揭示了新的思路。Qiao等[91]构建了负载糖酵解抑制剂3PO的黑磷纳米片BO (图3D), 在超声照射下, BO可产生ROS破坏肿瘤和肿瘤血管, 导致进一步缺氧和营养阻断; 此外, 释放的3PO抑制肿瘤糖酵解, 防止缺氧诱导的糖酵解和乳酸积累。SDT和3PO都可以切断乳酸的来源, 并通过阻断ATP的供给实现抗肿瘤的饥饿治疗。此外, 饥饿处理和SDT相结合, 进一步促进树突状细胞 (dendritic cells, DC) 的成熟, 促进DC的抗原呈递, 诱导抗肿瘤免疫治疗, 抑制肿瘤的生长, 提供了抑制糖酵解联合声动力疗法和免疫疗法抗肿瘤的新思路。

5 总结与展望

本文通过归纳总结肿瘤有氧糖酵解的作用机制及潜在靶点、具有调节有氧糖酵解作用的药物及基于糖酵解的纳米药物递送系统用于抑制糖酵解与其他治疗方式的肿瘤联合治疗, 为肿瘤有氧糖酵解的进一步研究和临床应用提供一定的参考。研究表明, 纳米药物递送系统用于调节肿瘤有氧糖酵解时, 一方面通过直接靶向肿瘤有氧糖酵解过程中涉及的关键酶、信号因子、信号通路及反应产物, 能够有效组织肿瘤细胞的生长、增殖、转移及免疫逃逸; 另一方面直接调节有氧糖酵解所造成的缺氧和酸性的肿瘤微环境也能够在一定程度上抑制有氧糖酵解, 进而提升抗肿瘤作用。随着纳米医学的不断发展, 纳米药物递送系统负载具有糖酵解调节作用的药物、关键酶抑制剂等其他糖酵解抑制剂外, 搭载叶酸、透明质酸、抗体等靶向配体有助于其在肿瘤部位高效富集, 使纳米药物递送系统在调节肿瘤有氧糖酵解的同时发挥出更大的抗肿瘤价值。

尽管纳米药物递送系统在调节肿瘤有氧糖酵解代谢过程中取得了一定成就, 然而仍存在一些挑战和困境需要解决。例如, 单一地调节肿瘤有氧糖酵解无法彻底杀死肿瘤细胞, 而联合治疗时, 由于糖酵解涉及肿瘤细胞内的多种生物合成途径, 破坏糖酵解可能使肿瘤对其他可用的治疗方法更脆弱和敏感[16,17]。此外, 尽管基于糖酵解的纳米药物递送系统在肿瘤治疗和诊断方面取得了进展, 但基于糖酵解的纳米药物递送系统的研究大多集中于基础理论, 仅在动物模型中完成验证, 可能限制未来的大规模生产和临床应用, 在临床转化中面临着一定的困难。因此, 仍需要建立更加安全、高效的基于糖酵解的纳米药物递送系统, 以促进临床转化为有效的疾病诊断和治疗策略。

作者贡献: 李一菁负责文章资料收集与撰写; 黄胜楠负责文章选题、构思及指导; 王子昂、直炜炜负责文献分析及格式修改; 祝侠丽为文章提供改进建议; 黄胜楠、祝侠丽为该文章的共同负责人。所有作者阅读并认可终稿。

利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Yuan ZN, Li YP, Zhang SF, et al. Extracellular matrix remodeling in tumor progression and immune escape: from mechanisms to treatments [J]. Mol Cancer, 2023, 22: 48.

[2] De Visser KE, Joyce JA. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth [J]. Cancer Cell, 2023, 41: 374-403.

[3] Han KS, Ren T, Li D, et al. Research progress in the application of mesoporous silica nanoparticles in tumor therapy [J]. Chem Reagents (化学试剂), 2023, 45: 1-10.

[4] Qu J, Yan S, Lei LTY, et al. Application of mitochondrial targeting strategy of nano-delivery system in tumor diagnosis and treatment [J]. Prog Biochem Biophys (生物化学与生物物理进展), 2024, 51: 70-81.

[5] Wang YH, Patti GJ. The Warburg effect: a signature of mitochondrial overload [J]. Trends Cell Biol, 2023, 33: 1014-1020.

[6] Deberardinis RJ, Chandel NS. We need to talk about the Warburg effect [J]. Nat Metab, 2020, 2: 127-129.

[7] Yadav D, Yadav A, Bhattacharya S, et al. GLUT and HK: two primary and essential key players in tumor glycolysis [J]. Semin Cancer Biol, 2024, 100: 17-27.

[8] Zhu B, Chen SY, Song MM. Advances of nanocarrier-based drug delivery system in chemotherapy-based combination therapy [J]. Chin Bull Life Sci (生命科学), 2023, 35: 437-447.

[9] Guan P, Meng ZX, Liu XR, et al. A biomimetic mineralization nanosystem based on glycolysis-oxidative stress-autophagy regulation for the suppression of malignant tumor and lung metastasis [J]. Chem Eng J, 2023, 468: 143730.

[10] Li XL, Duan ZY, Chen XT, et al. Impairing tumor metabolic plasticity *via* a stable metal-phenolic-based polymeric nanomedicine to suppress colorectal cancer [J]. Adv Mater, 2023, 35: e2300548.

[11] Paul S, Ghosh S, Kumar S. Tumor glycolysis, an essential sweet tooth of tumor cells [J]. Semin Cancer Biol, 2022, 86: 1216-1230.

[12] Menchikov LG, Shestov AA, Popov AV. Warburg effect revisited: embodiment of classical biochemistry and organic chemistry. current state and prospects [J]. Biochemistry (Mosc), 2023, 88: S1-S20.

[13] Wang N, Zhou YL, Song FX, et al. Research progress on the relationship between tumor glycolysis and tumor immune microenvironment [J]. Oncol Prog (癌症进展), 2022, 20: 1194-1197.

[14] Rodríguez-Enríquez S, Carreño-Fuentes L, Gallardo-Pérez JC, et al. Oxidative phosphorylation is impaired by prolonged hypoxia in breast and possibly in cervix carcinoma [J]. Int J Biochem Cell Biol, 2010, 42: 1744-1751.

[15] Zhang JF, Yang JY, Lin CY, et al. Endoplasmic reticulum stress-dependent expression of ERO1L promotes aerobic glycolysis in pancreatic cancer [J]. Theranostics, 2020, 10: 8400-8414.

[16] Domiński A, Krawczyk M, Konieczny T, et al. Biodegradable pH-responsive micelles loaded with 8-hydroxyquinoline glyco-conjugates for Warburg effect based tumor targeting [J]. Eur J Pharm Biopharm, 2020, 154: 317-329.

[17] Gu ZY, Yu CZ. Harnessing bioactive nanomaterials in modulating tumor glycolysis-associated metabolism [J]. J Nanobiotechnology, 2022, 20: 528.

[18] Geng CC, Pang SY, Ye RY, et al. Glycolysis-based drug delivery nanosystems for therapeutic use in tumors and applications [J]. Biomed Pharmacother, 2023, 165: 115009.

[19] Infantino V, Santarsiero A, Convertini P, et al. Cancer cell metabolism in hypoxia: role of HIF-1 as key regulator and therapeutic target [J]. Int J Mol Sci, 2021, 22: 5703.

[20] Yu L, Chen X, Sun XQ, et al. The glycolytic switch in tumors: how many players are involved? [J]. J Cancer, 2017, 8: 3430-3440.

[21] Bao XT, Zhang JH, Huang GM, et al. The crosstalk between HIFs and mitochondrial dysfunctions in cancer development [J]. Cell Death Dis, 2021, 12: 215.

[22] Wang YN, Wang YJ, Zhang Y. Role of HIF-1*α* in glycolysis of cancer cells [J]. J China Med Univ (中国医科大学学报), 2023, 52: 644-648.

[23] Manuelli V, Pecorari C, Filomeni G, et al. Regulation of redox signaling in HIF-1-dependent tumor angiogenesis [J]. FEBS J, 2022, 289: 5413-5425.

[24] Kierans SJ, Taylor CT. Regulation of glycolysis by the hypoxia-inducible factor (HIF): implications for cellular physiology [J]. J Physiol, 2021, 599: 23-37.

[25] Zhang PF, Cao LM, Fan PS, et al. LncRNA-MIF, a c-Myc-activated long non-coding RNA, suppresses glycolysis by promoting Fbxw7-mediated c-Myc degradation [J]. EMBO Rep, 2016, 17: 1204-1220.

[26] Pate KT, Stringari C, Sprowl-Tanio S, et al. Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer [J]. EMBO J, 2014, 33: 1454-1473.

[27] Wei Z, Ayishita NRJ, Liu Z, et al. Research progress on the role of lactic acid in tumor growth, metastasis, immunosuppression and immunotherapy [J]. Shandong Med J (山东医药), 2023, 63: 90-93.

[28] Yang YY, Huang J, Liu XY, et al. Screening of key target molecules for lactic acid regulation of M2-type polarization of mouse macrophages [J]. Chin J Immunol (中国免疫学杂志), 2023, 39: 2041-2048.

[29] Liu QL, Luo MC, Huang CH, et al. Epigenetic regulation of epithelial to mesenchymal transition in the cancer metastatic cascade: implications for cancer therapy [J]. Front Oncol, 2021, 11: 657546.

[30] Brand A, Singer K, Koehl GE, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells [J]. Cell Metab, 2016, 24: 657-671.

[31] Apicella M, Giannoni E, Fiore S, et al. Increased lactate secretion by cancer cells sustains non-cell-autonomous adaptive resistance to MET and EGFR targeted therapies [J]. Cell Metab, 2018, 28: 848-865.e6.

[32] Kumagai S, Koyama S, Itahashi K, et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments [J]. Cancer Cell, 2022, 40: 201-218.e9.

[33] Wang C, Xue LX, Zhu WQ, et al. Lactate from glycolysis regulates inflammatory macrophage polarization in breast cancer [J]. Cancer Immunol Immunother, 2023, 72: 1917-1932.

[34] Xu WX, Weng JL, Xu MH, et al. Functions of key enzymes of glycolytic metabolism in tumor microenvironment [J]. Cell Reprogram, 2023, 25: 91-98.

[35] Gómez-Escudero J, Clemente C, García-Weber D, et al. PKM2 regulates endothelial cell junction dynamics and angiogenesis *via* ATP production [J]. Sci Rep, 2019, 9: 15022.

[36] Xia Y, Wang X, Liu Y, et al. PKM2 is essential for bladder cancer growth and maintenance [J]. Cancer Res, 2022, 82: 571-585.

[37] Serganova I, Cohen IJ, Vemuri K, et al. LDH-A regulates the tumor microenvironment *via* HIF-signaling and modulates the immune response [J]. PLoS One, 2018, 13: e0203965.

[38] Zhang HF, Zhang K, Qiu LQ, et al. Cancer-associated fibroblasts facilitate DNA damage repair by promoting the glycolysis in non-small cell lung cancer [J]. Biochim Biophys Acta Mol Basis Dis, 2023, 1869: 166670.

[39] Hong XT, Zhong LH, Xie YR, et al. Matrine reverses the warburg effect and suppresses colon cancer cell growth *via* negatively regulating HIF-1*α* [J]. Front Pharmacol, 2019, 10: 1437.

[40] Li XP, Sun J, Xu QH, et al. Oxymatrine inhibits colorectal cancer metastasis *via* attenuating PKM2-mediated aerobic glycolysis [J]. Cancer Manag Res, 2020, 12: 9503-9513.

[41] Long L, Xiong W, Lin FW, et al. Regulating lactate-related immunometabolism and EMT reversal for colorectal cancer liver metastases using shikonin targeted delivery [J]. J Exp Clin Cancer Res, 2023, 42: 117.

[42] Zhang F, Chu ML, Zhao Q, et al. Effects of shikonin on glycolytic metabolism and biological characteristics of gastric cancer cells [J]. J Chin Med Mater (中药材), 2023, 46: 1249-1254.

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

[44] Gao J, Wang F, Hu LJ. EGCG inhibits glycolysis of pancreatic cancer cells *via* PI3K/Akt pathway [J]. Chin J Surg Integr Tradit

West Med (中国中西医结合外科杂志), 2023, 29: 677-681.

[45] Lian L, Yang ZJ, Yang B, et al. Effeets of quercetin on invasion and mobility of thyroid cancer TPC-1 cellsby inhibiting Akt-mTOR dependent glycolysis pathway [J]. Chin J Cancer Prev Treat (中华肿瘤防治杂志), 2023, 30: 639-646, 661.

[46] Zhou T, Zhang XX, Zhang GH, et al. Study on the mechanism of salidroside against gallbladder cancer mediated by Warburg effect *via* ERK/HIF-1α pathway [J]. J Chin Med Mater (中药材), 2023, 46: 1537-1541.

[47] Sun JL, Wang J, Xue XW, et al. Inhibition of proliferation and glycolysis of cervical cancer cells by kaempferol blocking JAK2/STAT3 pathway [J]. Pharm Biotechnol (药物生物技术), 2023, 30: 368-373.

[48] Fu R, Cao B, Wang TS. Mechanisms of the effect of diosgenin on the cellular biologicalprocesses of lung cancer cells [J]. Biotechnol (生物技术), 2023, 33: 616-620.

[49] Liu L, Peng Q, Wu ZM, et al. Inhibitory effect and its mechanism of evodiamine on tumor vascular proliferation [J]. Her Med (医药导报), 2023, 42: 1305-1311.

[50] Yin X, Hou YC, Yang LJ. Effeet of ginkgolide B on the proliferation and glycolysis level of esophageal cancer cells based on JAK2/STAT3 signaling pathway [J]. Mod Interv Diagn Treat Gastroenterol (现代消化及介入诊疗), 2023, 28: 442-446.

[51] Qu YQ, Zhang QY, Tan XY, et al. Effect of nuciferine against the proliferation of cholangiocarcinomacells through Akt/mTOR/4EBPl-glycolytic pathway [J]. Nat Prod Res Dev (天然产物研究与开发), 2023, 35: 1297-1304, 1379.

[52] Zhang HY. To Investigate the Effect and Mechanism of Curcumin on the Glycolysis of Lung Cancer A549 Cells based on NF-κB-Snail/HK3 Pathway (基于NF-κB-Snail/HK3途径探讨姜黄素对肺癌A549细胞糖酵解的干预作用及机制) [D]. Shenyang: Liaoning University of Traditional Chinese Medicine, 2023.

[53] Wu HY, Zhou SK, Wang CT, et al. Effects of deoxyelephantopin on proliferation, migration and glycolysis of hepatocellular carcinoma HepG2 cells [J]. Chin Tradit Pat Med (中成药), 2023, 45: 208-212.

[54] Zhang HY, Zhu BJ, Fan YF, et al. Effects of onychin on the glycolysis, proliferation, migration and invasion of lung cancer A549 cells *via* circ 0136666/miR-370 axis [J]. Anti-Tumor Pharm (肿瘤药学), 2022, 12: 745-751.

[55] Liu JX, Li YM. Effects of tanshinone II A on proliferation, metabolism and apoptosis of human cervical cancer SiHa cells [J]. Chin J Lab Diagn (中国实验诊断学), 2022, 26: 1369-1374.

[56] Zhang YX, Gui HM, Fan N, et al. Effects of oridonin regulating miR-4735-3p through circLRBA on the biological function and glycolysis of bladder cancer [J]. J Toxicol (毒理学杂志), 2022, 36: 224-230.

[57] Yu PP, Jin XS. Effects of Juglone on proliferation, invasion and glycolysis ofastric cancer cell line SGC-7901 [J]. Chin J Tradit Med Sci Technol (中国中医药科技), 2022, 29: 761-766.

[58] Li L, Deng DJ, Tan XY, et al. Mechanism of cucurbitacin B in regulating glyeolysis and inhibiting proliferation of HuCCT1 cells [J]. Chin J Exp Tradit Med Form (中国实验方剂学杂志), 2022, 28: 74-81.

[59] Dong JS, Zhao JF, Zhang LC, et al. Effects of erianin on glycolysis, proliferation, migration and invasion of prostate cancer cells by regulating lncRNA LINC01354/miR-515-5p [J]. Chin Tradit Pat Med (中成药), 2022, 44: 2688-2693.

[60] Liu YQ. Artemisinin regulates Warburg effect of cervicalcancer cells by inhibiting SIRT2 [J]. J Shenyang Pharm Univ (沈阳药科大学学报), 2022, 39: 1111-1117, 1129.

[61] Deng DJ, Li L, Tan XY, et al. Effect and mechanism of icaritin on inhibiting proliferation of intrahepatic cholangiocarcinoma cells by Akt/mTOR-mediated glycolysis [J]. Chin Tradit Herb Drugs (中草药), 2022, 53: 3061-3069.

[62] Fan Q, Yang C, Liu YS. Molecular mechanism of withaferin a regulating glycolysis, proliferation, migration and invasion of breast cancer MDA-MB-231 cells through the circOSBPL10/miR-128-3p pathway [J]. Tianjin J Tradit Chin Med (天津中医药), 2022, 39: 801-808.

[63] Peng JM, He ZJ, Yuan YQ, et al. Docetaxel suppressed cell proliferation through Smad3/HIF-1α -mediated glycolysis in prostate cancer cells [J]. Cell Commun Signal, 2022, 20: 194.

[64] Zhang L, Li Q, Jiang S, et al. 1,25-Dihydroxyvitamin D_3 promotes apoptosis in human breast cancer MCF-7cells by glycolysis pathway [J]. Chin J Cancer Biother (中国肿瘤生物治疗杂志), 2023, 30: 784-788.

[65] Qi J, Wu QC, Zhu XQ, et al. Propofol attenuates the adhesion of tumor and endothelial cells through inhibiting glycolysis in human umbilical vein endothelial cells [J]. Acta Biochim Biophys Sin (Shanghai), 2019, 51: 1114-1122.

[66] Cheng Y, Li SM, Dang CX, et al. Study of glucose transporter type 1 enhances esophageal cancer cell sensitivity to 2-deoxyglucose treatment [J]. World Clin Drug (世界临床药物), 2020, 41: 253-260.

[67] Roy S, Dukic T, Bhandary B, et al. 3-Bromopyruvate inhibits pancreatic tumor growth by stalling glycolysis, and dismantling mitochondria in a syngeneic mouse model [J]. Am J Cancer Res, 2022, 12: 4977-4987.

[68] Liu YM, Tang KW, Chen F, et al. Progress in improving the stability of volatile oil of traditional Chinese medicine by nano drug delivery system [J]. Lishizhen Med Mater Med Res (时珍国医国药), 2023, 34: 1714-1716.

[69] Xu QQ, Yang SY, Cui L, et al. Progress in application of nano-drug delivery system responsive to tumor microenvironment [J]. Chin J New Drugs Clin Rem (中国新药与临床杂志), 2023, 42: 216-221.

[70] Sun L, Liu YQ, Yang NY, et al. Gold nanoparticles inhibit tumor growth *via* targeting the Warburg effect in a c-Myc-dependent way [J]. Acta Biomater, 2023, 158: 583-598.

[71] Ruan SR, Yin WM, Chang J, et al. Acidic and hypoxic tumor microenvironment regulation by CaO_2-loaded polydopamine nanoparticles [J]. J Nanobiotechnology, 2022, 20: 544.

[72] Wu SX, Zhang KX, Liang Y, et al. Nano-enabled tumor systematic energy exhaustion *via* Zinc (II) interference mediated glycolysis inhibition and specific GLUT1 depletion [J]. Adv Sci (Weinh), 2022, 9: e2103534.

[73] Wang G, Yu Y, Wang YZ, et al. The effects and mechanisms of isoliquiritigenin loaded nanoliposomes regulated AMPK/mTOR mediated glycolysis in colorectal cancer [J]. Artif Cells Nanomed Biotechnol, 2020, 48: 1231-1249.

[74] Wang G, Yu Y, Wang YZ, et al. Effects and mechanisms of fatty acid metabolism-mediated glycolysis regulated by betulinic acid-loaded nanoliposomes in colorectal cancer [J]. Oncol Rep, 2020, 44: 2595-2609.

[75] Chen WH, Luo GF, Lei Q, et al. Overcoming the heat endurance of tumor cells by interfering with the anaerobic glycolysis metabolism for improved photothermal therapy [J]. ACS Nano, 2017, 11: 1419-1431.

[76] Fang XL, Akrofi R, Yang H, et al. The NIR inspired nano-CuSMn(II) composites for lactate and glycolysis attenuation [J]. Colloids Surf B Biointerfaces, 2019, 181: 728-733.

[77] Liu XH, Li YH, Wang KY, et al. GSH-responsive nanoprodrug to inhibit glycolysis and alleviate immunosuppression for cancer therapy [J]. Nano Lett, 2021, 21: 7862-7869.

[78] Cao YS, Yang H. Research progress of glucose oxidase-mediated multimodal cancer therapy [J]. J Shanghai Norm Univ (Nat Sci) [上海师范大学学报 (自然科学版)], 2021, 50: 764-773.

[79] Fu LH, Qi C, He J, et al. Research advances in glucose oxidase-based multimodal synergistic cancer therapy [J]. Sci China C (中国科学: 生命科学), 2021, 51: 850-870.

[80] Zhang H, Liu RH, Wan P, et al. Targeting tumor energy metabolism *via* simultaneous inhibition of mitochondrial respiration and glycolysis using biodegradable hydroxyapatite nanorods [J]. Colloids Surf B Biointerfaces, 2023, 226: 113330.

[81] Yu WQ, Lin RY, He XQ, et al. Self-propelled nanomotor reconstructs tumor microenvironment through synergistic hypoxia alleviation and glycolysis inhibition for promoted anti-metastasis [J]. Acta Pharm Sin B, 2021, 11: 2924-2936.

[82] Chu Q, Liao LH, Liu B, et al. Sulfite-inserted MgAl layered double hydroxides loaded with glucose oxidase to enable SO_2-mediated synergistic tumor therapy [J]. Adv Funct Mater, 2021, 31: 2103262.

[83] Zang SY, Huang KX, Li JX, et al. Metabolic reprogramming by dual-targeting biomimetic nanoparticles for enhanced tumor chemo-immunotherapy [J]. Acta Biomater, 2022, 148: 181-193.

[84] Yi XL, Duan QY, Wu FG. Low-temperature photothermal therapy: strategies and applications [J]. Research (Wash D C), 2021, 2021: 9816594.

[85] Dai YN, Sun ZQ, Zhao HH, et al. NIR-II fluorescence imaging guided tumor-specific NIR-II photothermal therapy enhanced by starvation mediated thermal sensitization strategy [J]. Biomaterials, 2021, 275: 120935.

[86] Ding XL, Liu MD, Cheng Q, et al. Multifunctional liquid metal-based nanoparticles with glycolysis and mitochondrial metabolism inhibition for tumor photothermal therapy [J]. Biomaterials, 2022, 281: 121369.

[87] Cao XS, Li MX, Liu QY, et al. Inorganic sonosensitizers for sonodynamic therapy in cancer treatment [J]. Small, 2023, 19: e2303195.

[88] Nguyen Cao TG, Truong Hoang Q, Kang JH, et al. Bioreducible exosomes encapsulating glycolysis inhibitors potentiate mitochondria-targeted sonodynamic cancer therapy *via* cancer-targeted drug release and cellular energy depletion [J]. Biomaterials, 2023, 301: 122242.

[89] Hua JF, Wu P, Gan L, et al. Current strategies for tumor photodynamic therapy combined with immunotherapy [J]. Front Oncol, 2021, 17: 738323.

[90] Zhang P, Li Z, Cao WL, et al. A PD-L1 antibody-conjugated PAMAM dendrimer nanosystem for simultaneously inhibiting glycolysis and promoting immune response in fighting breast cancer [J]. Adv Mater, 2023, 35: e2305215.

[91] Qiao K, Luo C, Huang R, et al. Ultrasound triggered tumor metabolism suppressor induces tumor starvation for enhanced sonodynamic immunotherapy of breast cancer [J]. Int J Nanomedicine, 2023, 18: 3801-3811.