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·综 述·

糖代谢重编程在卵巢癌化疗耐药中作用的研究进展

Research progress in the role of glucose metabolism reprogramming in chemotherapy resistance of ovarian cancer

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[摘 要] 卵巢癌(OC)是最为致命的妇科恶性肿瘤,5年生存率仅为40%,而化疗耐药是影响OC患者预后的重要因素之一。研究发现糖代谢重编程参与肿瘤化疗耐药,其中涉及有氧糖酵解及磷酸戊糖途径代谢酶的过度表达而促进耐药,并且细胞氧化磷酸化状态也与化疗耐药密切相关,目前这些代谢途径中的关键分子已被用做新的药物靶点,并与传统抗肿瘤药物联合使用,在临床前研究中展现出良好的应用潜力。糖代谢重编程在OC化疗耐药中发挥重要作用,了解新型靶向代谢药物及其相关的治疗进展,对探索OC化疗耐药机制具有重要意义,可能为OC治疗提供新的治疗策略。

[关键词] 卵巢癌;化疗耐药;糖代谢重编程;Warburg效应;小分子抑制剂
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肿瘤的发生发展不仅涉及细胞增殖失控,能量代谢的变化亦会促进肿瘤细胞的生长与分裂。当致瘤突变发生或其他因素导致细胞常规代谢途径的活性增强或抑制,此现象称为代谢重编程。最早发现的代谢重编程现象称为Warburg效应,即有氧糖酵解,癌细胞也很容易通过有氧糖酵解来消耗和代谢葡萄糖。有氧糖酵解与氧化磷酸化、磷酸戊糖途径共同作用从而改变葡萄糖代谢途径,影响癌细胞对化疗药物的反应[1]。Warburg效应为肿瘤细胞提供了生物合成途径的中间体,包括用于核苷酸合成的核糖、甘油、柠檬酸盐和用于脂质合成的非必需氨基酸[2]。Warburg效应并非线粒体功能障碍所致,而是在缺氧诱导因子1(hypoxia inducible factor-1,HIF-1)过度表达[3]、癌基因激活和肿瘤抑制因子功能失活[4]、肿瘤微环境[5]及表观遗传学修饰[6]等多种因素作用下发生的。因此,HANAHAND[7]将代谢重编程定义为癌症的标志之一。研究[8]显示,卵巢癌(ovarian cancer,OC)细胞并非仅维持糖酵解这一代谢途径,可能存在其他代谢途径或偏好。探索OC耐药细胞的代谢特征有助于完善OC细胞对药物的代谢理论基础,通过调节癌细胞的代谢来改善其对化疗药物的反应,可能为OC治疗提供新的治疗策略。

1 OC的糖代谢重编程

鉴于OC的异质性,瘤间和瘤内可能出现不同代谢偏好。OC耐药细胞代谢偏好主要包括:一是糖酵解显著增加的细胞,如顺铂耐药细胞A2780/DDP具有较低的氧化磷酸化水平,其糖酵解酶水平、葡萄糖摄取及乳酸水平高于顺铂敏感的OC细胞A2780[9];二是氧化磷酸化占据优势的细胞,如顺铂耐药细胞PEA2具有较低的整体葡萄糖代谢,其糖酵解酶和糖酵解能力水平较低,细胞外酸化率较低,但氧化磷酸化高于顺铂敏感细胞PEA1[10];三是糖酵解和氧化磷酸化代谢活性同时增强的细胞,如C200和PEO4[11]。研究[12-13]表明,OC患者的组织和血液较健康人表现出更高的糖酵解活性,其参与三羧酸循环和氧化磷酸化的酶也有所增加,包括丙酮酸脱氢酶、柠檬酸合酶和异柠檬酸脱氢酶[14]。在不同病理类型的OC中,高级别浆液性癌与其他类型相比显示出更高的葡萄糖转运蛋白和糖酵解酶水平,且晚期OC糖酵解活性高于早期[15];高级别浆液性癌组织也比低级别浆液性癌更依赖于氧化磷酸化[10]。高级别浆液性癌和透明细胞癌等侵袭性更强的组织学类型比侵袭性低的类型表现出更多的糖酵解活性[16]。

2 糖代谢重编程对OC耐药的影响

糖代谢重编程不仅可增强肿瘤细胞增殖和存活的潜能,还可通过多种途径促进肿瘤的增殖、转移和耐药[17]。Warburg效应能够减少活性氧的产生,提高细胞抗氧化能力,减少细胞凋亡[18]。Warburg效应产生的乳酸和磷酸戊糖途径产生的CO_2的分解代谢物堆积导致胞外酸性环境,并对OC细胞的耐药性产生

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影响，例如转运蛋白P-糖蛋白（p-glycoprotein，p-gp）介导的多药耐药性可能依赖于pH值的变化[19]。胞外酸性环境也会增强将化疗药物排出细胞外的外排泵的功能[20]。癌细胞膜双侧的反向pH梯度可以减少弱碱性抗癌药物如蒽环类药物向胞内的扩散[21]。此外，过高的糖酵解及乳酸水平也会导致癌细胞调节免疫细胞浸润进而降低免疫治疗的有效性[22-23]。

研究[15, 24]发现，有氧糖酵解在OC耐药细胞中被激活，但也有研究[11, 25-26]发现，在耐药细胞中存在有氧糖酵解转向氧化磷酸化的现象。OC有氧糖酵解及氧化磷酸化的活性主要受生长因子信号通路、PI3K/Akt/mTORC1通路、Myc癌基因和HIF-1α通路等多种信号通路的调节[27]。

治疗OC的多种细胞毒性药物能够干扰葡萄糖代谢引起细胞毒性。化疗药物顺铂能够将癌细胞从有氧糖酵解状态重新定向至氧化磷酸化，使癌细胞从有氧糖酵解中获得的代谢减少，并且顺铂还能下调己糖激酶、丙酮酸脱氢酶激酶等参与有氧糖酵解酶的表达[28]。化疗药物紫杉醇可影响糖酵解，降低ATP水平并抑制癌细胞活力[29]。研究证明，糖酵解影响肿瘤靶向药物耐药的主要机制是抑制肿瘤细胞凋亡[30]、促进上皮-间质转化[31]及诱导自噬[32]。

2.1　糖酵解代谢酶过度表达促进OC耐药性

多种糖代谢关键酶的异常表达可导致肿瘤耐药性[33]。己糖激酶（hexokinase, HK）是糖酵解过程中的第一个限速酶。HK2促进糖酵解和抑制凋亡，并在高级别浆液性OC中表达升高[15]。HK2高表达与OC化疗耐药相关，下调其表达影响OC细胞对顺铂的敏感性，其机制可能是增强药物诱导的ERK1/2磷酸化和自噬活性[34]。p53作为HK2的负调节因子，可通过抑制HK2表达提高OC化疗敏感性[35]。体内实验[36]表明，HK2的缺失能够降低小鼠模型的肿瘤负荷并延长生存期。

磷酸果糖激酶（phosphofructokinase，PFK）在糖酵解过程中催化6-磷酸果糖磷酸化，PFK及其调节因子也参与OC的糖酵解和化疗耐药。6-磷酸果糖-2-激酶（6-phosphofructose-2-kinase，PFKFB）是控制果糖-2，6-二磷酸水平的双功能酶家族，由于果糖-2，6-二磷酸是控制PFK活性的重要下游代谢物，因此PFKFB也对PFK起到调节作用。下调PFKFB2表达可增强p53野生型OC细胞HeyA8和A2780对紫杉醇化疗药物的敏感性，PFKFB2可以作为表达p53野生型上皮性OC新的治疗靶点[37]。PFKFB3在OC中上调，是化疗耐药、复发和预后的潜在生物标志物[38]。

丙酮酸激酶（pyruvate kinase，PKM）是催化糖酵解的最后一个不可逆步骤。高表达的PKM2与肿瘤生长相关，是OC预后不良的因素之一[39]。用于晚期OC维持治疗的多聚ADP核糖聚合酶（poly ADP-ribose polymerase，PARP）抑制剂可抑制癌细胞中断裂DNA的同源重组修复，而PKM2通过影响DNA损伤应答蛋白表达促进DNA同源重组修复。抑制PKM2能增强OC细胞对化疗药物奥拉帕利的敏感性并诱导癌细胞的DNA损伤[40]。相比于单独沉默多药耐药基因1（multidrug resistance-1，MDR-1），同时沉默PKM2和MDR-1基因可显著提高紫杉醇对多药耐药OC的疗效[41]。

丙酮酸脱氢酶激酶（pyruvate dehydrogenase kinase，PDK）是丙酮酸脱氢酶复合物的调节酶。PDK1可诱导OC细胞对顺铂的耐药，在耐药细胞中下调PDK1可增强其对顺铂诱导的细胞死亡的敏感性，其机制与表皮生长因子受体（epithelial growth factor receptor，EGFR）的磷酸化增加有关[42]。PDK2和PDK4通过抑制线粒体氧化磷酸化促进顺铂耐药，PDK4高表达与OC患者较差的总生存率和无进展生存率相关[43-44]。PDK抑制剂的使用已在多种癌症模型中显示出显著的抑制肿瘤生长的作用[45-47]。靶向PDK可能是治疗耐药上皮性OC的潜在方法。

乳酸脱氢酶（lactate dehydrogenase，LDH）是参与糖酵解催化丙酮酸还原的又一重要的酶。IKEDA等[48]实验结果证明，血清中高水平的LDH是上皮性OC顺铂耐药和不良预后的预测因素。敲低LDH或使用其抑制剂Oxamate不仅能提高癌细胞对PARP抑制剂的敏感性，还可显著促进PARP抑制剂对肿瘤生长的抑制作用[49-50]。

由此可见，有氧糖酵解通过促进多种关键酶的表达显著促进疾病进展和化疗耐药性，其中的关键节点成为多种新型小分子抑制剂的研发目标。

2.2　磷酸戊糖途径代谢酶过度表达促进OC耐药

OC耐药细胞不仅表现出葡萄糖摄取及消耗增加，磷酸戊糖途径中葡萄糖-6-磷酸脱氢酶（glucose-6-phosphate dehydrogenase，G6PD）的表达及活性也会增加[51]。抑制G6PD表达可恢复肿瘤耐药细胞对顺铂的敏感性，G6PD抑制剂和顺铂联合治疗可显著增强顺铂的细胞毒性和对耐药细胞的敏感性[52-53]；利用OC异种移植瘤模型同样证实了二者联合治疗不仅可显著抑制肿瘤增殖，而且可清除小鼠的腹膜转移[54]。此外，有研究[55]还发现，G6PD促进紫杉醇的耐药性，在紫杉醇耐药细胞中，STAT3结合G6PD的启动子区域，可促进G6PD表达，激活磷酸戊糖代谢途

径，使肿瘤细胞增殖增加及对紫杉醇化疗耐药。抑制G6PD表达可使紫杉醇耐药细胞对紫杉醇治疗重新敏感，其机制可能是G6PD通过激活内质网关键蛋白进而调节线粒体外膜透化作用来促进谷胱甘肽S-转移酶P1（glutathione S-transferase P1,GSTP1）的表达，而GSTP1在胞内通过与谷胱甘肽结合发挥解毒作用从而促进耐药[56]。

因此，磷酸戊糖途径的代谢变化也是影响OC化疗耐药的重要因素之一，进一步的研究能为临床的靶向代谢治疗提供实验基础和理论依据。

2.3 氧化磷酸化状态对OC耐药的影响

最初认为癌细胞对糖酵解的依赖性是由于线粒体功能受到损伤，但近年来研究[16]表明，氧化磷酸化也是癌细胞的能量代谢形式之一。晚期OC的碳源分布不均匀，主要分为低氧和高氧氧化磷酸化。低氧表现为糖酵解代谢；而高氧则表现为电子传递链成分水平升高和线粒体呼吸增强，并表现出慢性氧化应激[57]。代谢分析[26]显示，耐药性OC细胞倾向氧化磷酸化的代谢转变，此种转变与线粒体网络重组相协调，并积累线粒体成分。氧化磷酸化状态的增强可能导致OC细胞对氧化磷酸化抑制的抵抗性减弱，高氧的晚期OC更容易受到线粒体复合物Ⅰ抑制剂二甲双胍的影响，且对常规化疗的反应增强[58]。二甲双胍和复合物Ⅴ抑制剂寡霉素诱导OC细胞对顺铂重新敏感[11]。二甲双胍提高活性氧的产生并促进高氧化磷酸化的细胞群死亡，二甲双胍与顺铂联合应用可以抑制癌细胞的增殖，并增加耐药细胞系对顺铂的敏感性[59]，但二甲双胍对低氧化磷酸化的亚组癌细胞却几乎无作用。

总之，线粒体氧化磷酸化状态同样会影响OC细胞对化疗的反应，靶向线粒体氧化磷酸化的治疗方式可能是OC治疗策略中的重要一环。

3 OC糖代谢重编程靶向药物的研究进展

目前针对糖代谢重编程的靶向药物大多处于临床前基础研究阶段，将这些小分子抑制剂和传统化疗药物联合使用，在体内外实验中均展现出抑制肿瘤生长、克服OC化疗耐药的作用。

3.1 靶向糖酵解的小分子药物

此类药物主要针对葡萄糖转运酶和糖酵解限速酶[60]。葡萄糖转运蛋白（glucose transporter-1，GLUT-1）抑制剂BAY-876在OC细胞SKOV3、OVCAR3及异种移植瘤模型实验中显示出显著抑制肿瘤生长的作用[61]。此外，有实验研发了多种选择性葡萄糖摄取抑制剂，如chromopynone[62]、glutor[63]、glupin[63]及植物中提取的MAP30[64]。糖酵解限速酶HK2的选择性抑制剂2-脱氧葡萄糖（2-deoxy-glucose，2-DG）能够增强顺铂在OC细胞中的抗肿瘤作用，分析认为2-DG通过增加内质网应激和减少酸性囊泡中ATP的储存而增强癌细胞对顺铂的敏感性[65]。PFKFB3抑制剂PFK158能使葡萄糖摄取减少、ATP产生及乳酸释放减少，从而导致细胞凋亡。PFK158与化疗药物卡铂协同作用，可诱导自噬通量靶向耐药OC细胞从而改善耐药性[66]。

3.2 针对氧化磷酸化的治疗

针对氧化磷酸化的抑制剂主要包括抑制线粒体转移和线粒体动力学、降低线粒体功能的靶向药物、影响呼吸链调剂相关药物及呼吸链复合物抑制剂等[67]。抑制线粒体呼吸链复合物Ⅰ活性的二甲双胍在实验中显现出增强化疗药物敏感性的作用[59]。氧化应激诱导剂如阿托伐醌参与氧化还原并干扰泛醌介导的线粒体电子传递，现已逐渐应用于实体瘤的治疗[68]。研究[69]表明，阿托伐醌作用于OC细胞，会导致线粒体呼吸抑制、能量减少和氧化应激，从而克服OC耐药性。复合物Ⅳ抑制剂三氧化二砷与化疗药物奥拉帕利的联用能够发挥协同毒性，通过腺苷酸活化蛋白激酶α（adenylate-activated protein kinase α, AMPKα）-硬脂酰辅酶A去饱和酶-1（stearoyl-CoA desaturase 1，SCD1）的信号传导，增加对顺铂耐药的OC的细胞凋亡，并引发顺铂耐药OC细胞的铁死亡[70]。抑制HK2会抑制糖酵解并增强氧化磷酸化，使肿瘤细胞对二甲双胍敏感，沉默HK2联合二甲双胍可协同诱导细胞死亡并抑制肿瘤生长[71]。

由于OC优先利用有氧糖酵解及氧化磷酸化为癌细胞提供充足能量，针对线粒体氧化磷酸化和特定代谢偏好如糖酵解的协同抑制药物为抗肿瘤的策略开辟了新途径。

4 小 结

有氧糖酵解不仅能产生ATP，同时有利于增殖细胞所需的代谢合成反应，并且还可通过戊糖磷酸途径氧化分解产生的NADPH保护细胞免受氧化应激[72]，因此，Warburg效应被认为是癌症的标志之一。肿瘤细胞同时具有氧化磷酸化的能力，这体现其代谢可塑性和适应营养物质及氧气变化的能力。有氧糖酵解和磷酸戊糖途径代谢酶过度表达、线粒体氧化磷酸化状态均影响OC对化疗的反应。为了克服OC化疗耐药性，潜在干预策略是抑制OC细胞生长的首选代谢方式，但目前靶向糖代谢的药物在临床应用上仍存在局限性，由于许多代谢酶在正常组织

中也发挥生理功能，抑制此类代谢酶也可能产生难以避免的全身毒性作用[60]。鉴于OC的异质性，不仅需要进一步研究来确定这些策略在OC患者中的临床有效性，还须筛选生物标志物进行准确的亚组分类，识别出更多可能从靶向代谢药物的应用中获益的OC患者[57]，例如过氧化物酶体-增殖物激活受体γ辅激活因子（peroxisome-proliferator-activated receptor γ coactivator，PGC）-1α和b的高表达意味着OC患者对二甲双胍疗法的反应更好[73]。由于肿瘤细胞具有代谢可塑性，应格外注意靶向有氧糖酵解和氧化磷酸化治疗的协调性，避免出现由靶向单一代谢途径治疗导致靶向药物的耐药性[74]。

因此，进一步探究抑制氧化磷酸化和阻断糖酵解的机制及相关靶向药物研究或将给OC患者治疗带来新的突破。

[参 考 文 献]

[1] KUBIK J, HUMENIUK E, ADAMCZUK G, *et al*. Targeting energy metabolism in cancer treatment[J/OL]. Int J Mol Sci, 2022, 23(10): 5572[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC9146201/. DOI: 10.3390/ijms23105572.

[2] JAWORSKA M, SZCZUDŁO J, PIETRZYK A, *et al*. The Warburg effect: a score for many instruments in the concert of cancer and cancer niche cells[J]. Pharmacol Rep, 2023, 75(4): 876-890. DOI: 10.1007/s43440-023- 00504-1.

[3] LYU Y Y, ZHANG Y L, WANG Y H, *et al*. HIF-1α regulated WTAP overexpression promoting the Warburg effect of ovarian cancer by m^6A-dependent manner[J/OL]. J Immunol Res, 2022, 2022: 6130806[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC9207020/. DOI: 10.1155/2022/6130806.

[4] MURALI R, BALASUBRAMANIAM V, SRINIVAS S, *et al*. Deregulated metabolic pathways in ovarian cancer: cause and consequence[J/OL]. Metabolites, 2023, 13(4): 560[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC10141515/. DOI: 10.3390/metabo13040560.

[5] LIN Y, LIANG X, ZHANG X J, *et al*. Metabolic cross-talk between ovarian cancer and the tumor microenvironment-providing potential targets for cancer therapy[J/OL]. Front Biosci, 2022, 27(4): 139[2023-11-05]. https://www. imrpress. com/journal/FBL/27/4/10.31083/j. fbl2704139. DOI: 10. 31083/j. fbl2704139.

[6] ABI ZAMER B, ABUMUSTAFA W, HAMAD M, *et al*. Genetic mutations and non-coding RNA-based epigenetic alterations mediating the Warburg effect in colorectal carcinogenesis[J/OL]. Biology, 2021, 10(9): 847[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC8472255/. DOI: 10.3390/biology10090847.

[7] HANAHAN D. Hallmarks of cancer: new dimensions[J]. Cancer Discov, 2022, 12(1): 31-46. DOI: 10.1158/2159-8290.CD-21-1059.

[8] KOBAYASHI H. Recent advances in understanding the metabolic plasticity of ovarian cancer: a systematic review[J/OL]. Heliyon, 2022, 8(11): e11487[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC9668530/. DOI: 10.1016/j.heliyon.2022.e11487.

[9] ZHOU L, LIU L L, CHAI W, *et al*. Dichloroacetic acid upregulates apoptosis of ovarian cancer cells by regulating mitochondrial function[J/OL]. Onco Targets Ther, 2019, 12: 1729-1739[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC6419601/. DOI: 10.2147/OTT. S194329.

[10] MATASSA D S, AMOROSO M R, LU H, *et al*. Oxidative metabolism drives inflammation-induced platinum resistance in human ovarian cancer[J]. Cell Death Differ, 2016, 23(9): 1542-1554. DOI: 10.1038/cdd.2016.39.

[11] DAR S, CHHINA J, MERT I, *et al*. Bioenergetic adaptations in chemoresistant ovarian cancer cells[J/OL]. Sci Rep, 2017, 7(1): 8760[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC5562731/. DOI: 10. 1038/s41598-017-09206-0.

[12] LI N, LI H, WANG Y, *et al*. Quantitative proteomics revealed energy metabolism pathway alterations in human epithelial ovarian carcinoma and their regulation by the antiparasite drug ivermectin: data interpretation in the context of 3P medicine[J]. EOMA J, 2020, 11(4): 661-694. DOI: 10.1007/ s13167-020-00224-z.

[13] KERSLAKE R, PANFILOV S, MUSTAFA N, *et al*. Elevated circulating lactate levels and widespread expression of its cognate receptor, hydroxycarboxylic acid receptor 1 (HCAR1), in ovarian cancer[J/OL]. J Clin Med, 2022, 12(1): 217[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9821497/. DOI: 10.3390/jcm12010217.

[14] SIGNORILE A, DE RASMO D, CORMIO A, *et al*. Human ovarian cancer tissue exhibits increase of mitochondrial biogenesis and cristae remodeling[J/OL]. Cancers, 2019, 11(9): 1350[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC6770021/. DOI: 10.3390/cancers11091350.

[15] XINTAROPOULOU C, WARD C, WISE A, *et al*. Expression of glycolytic enzymes in ovarian cancers and evaluation of the glycolytic pathway as a strategy for ovarian cancer treatment[J/OL]. BMC Cancer, 2018, 18(1): 636[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987622/. DOI: 10.1186/s12885- 018-4521-4.

[16] NANTASUPHA C, THONUSIN C, CHAROENKWAN K, *et al*. Metabolic reprogramming in epithelial ovarian cancer[J/OL]. Am J Transl Res, 2021, 13(9): 9950-9973(Published online 2021 Sep 15)[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC8507042/.

[17] ZHANG Y Q, WANG Y N, ZHAO G Y, *et al*. Metabolic dependencies and targets in ovarian cancer[J/OL]. Pharmacol Ther, 2023, 245: 108413[2023-11-05]. https://www. sciencedirect. com/science/article/abs/pii/S0163725823000773?via%3Dihub. DOI: 10.1016/j.pharmthera.2023.108413.

[18] SHAH M A, ROGOFF H A. Implications of reactive oxygen species on cancer formation and its treatment[J]. Semin Oncol, 2021, 48(3): 238-245. DOI: 10.1053/j.seminoncol.2021.05.002.

[19] OMRAN Z, SCAIFE P, STEWART S, *et al*. Physical and biological characteristics of multi drug resistance (MDR): An integral approach considering pH and drug resistance in cancer[J/OL]. Semin Cancer Biol, 2017, 43: 42-48[2023-11-05]. https://www.sciencedirect. com/science/article/abs/pii/S1044579X17300020?via%3Dihub. DOI: 10.1016/j.semcancer.2017.01.002.

[20] KOLTAI T. The complex relationship between multiple drug resistance and the tumor pH gradient: a review[J/OL]. Cancer Drug Resist, 2022, 5(2): 277-303[2023-11-05]. https://www.ncbi.nlm.nih.

gov/pmc/ articles/PMC9255250/. DOI: 10.20517/cdr.2021.134.

[21] ZHITOMIRSKY B, ASSARAF Y G. Lysosomes as mediators of drug resistance in cancer[J/OL]. Drug Resist Updat, 2016, 24: 23-33 [2023-11-05]. https://www.sciencedirect.com/science/article/abs/pii/S1368764615000588?via%3Dihub. DOI: 10.1016/j.drup.2015.11.004.

[22] 李星晨, 邓红, 于津浦. 代谢重编程介导肿瘤免疫微环境重塑的现状和展望[J]. 中国肿瘤生物治疗杂志, 2022, 29(2): 87-92. DOI: 10.3872/j.issn.1007.385x2022.02.001.

[23] YIN T T, HUANG M X, WANG F, *et al*. Lactate score predicts survival, immune cell infiltration and response to immunotherapy in breast cancer[J/OL]. Front Genet, 2022, 13: 943849[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC9421043/. DOI: 10.3389/fgene.2022.943849.

[24] CHAKRABORTY P K, MUSTAFI S B, XIONG X H, *et al*. MICU1 drives glycolysis and chemoresistance in ovarian cancer[J/OL]. Nat Commun, 2017, 8: 14634[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC5477507/. DOI: 10.1038/ncomms14634.

[25] SRIRAMKUMAR S, SOOD R, HUNTINGTON T D, *et al*. Platinum-induced mitochondrial OXPHOS contributes to cancer stem cell enrichment in ovarian cancer[J/OL]. J Transl Med, 2022, 20(1): 246[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9153190/. DOI: 10.1186/s12967-022- 03447-y.

[26] ZAMPIERI L X, GRASSO D, BOUZIN C, *et al*. Mitochondria participate in chemoresistance to cisplatin in human ovarian cancer cells[J]. Mol Cancer Res, 2020, 18(9): 1379-1391. DOI: 10.1158/1541-7786.Mcr- 19-1145.

[27] WANG Y, XIE H, CHANG X H, *et al*. Single-cell dissection of the multiomic landscape of high-grade serous ovarian cancer[J]. Cancer Res, 2022, 82(21): 3903-3916. DOI: 10.1158/0008-5472. Can-21-3819.

[28] MACCIÒ A, MADEDDU C. Cisplatin: An old drug with a newfound efficacy--from mechanisms of action to cytotoxicity[J]. Expert Opin Pharmacother, 2013, 14(13): 1839-1857. DOI: 10.1517/14656566.2013. 813934.

[29] GAO M, YANG Y, GAO Y, *et al*. The anti-MDR efficacy of YAN against A549/Taxol cells is associated with its inhibition on glycolysis and is further enhanced by 2-deoxy-d-glucose[J/OL]. Chem Biol Interact, 2022, 354: 109843[2023-11-05]. https://www.sciencedirect.com/science/article/abs/pii/S0009279722000485?via%3Dihub. DOI: 10.1016/j.cbi.2022.109843.

[30] EFIMOVA E V, TAKAHASHI S, SHAMSI N A, *et al*. Linking cancer metabolism to DNA repair and accelerated senescence[J]. Mol Cancer Res, 2016, 14(2): 173-184. DOI: 10.1158/1541-7786.Mcr-15-0263.

[31] LEE S Y, JU M K, JEON H M, *et al*. Oncogenic metabolism acts as a prerequisite step for induction of cancer metastasis and cancer stem cell phenotype[J/OL]. Oxid Med Cell Longev, 2018, 2018: 1027453[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC6323533/. DOI: 10.1155/2018/1027453.

[32] LI W H, ZHOU C, YU L, *et al*. Tumor-derived lactate promotes resistance to bevacizumab treatment by facilitating autophagy enhancer protein RUBCNL expression through histone H3 lysine 18 lactylation (H3K18la) in colorectal cancer[J]. Autophagy, 2024: 20(1) 114-130 DOI: 10.1080/15548627.2023.2249762.

[33] DESBATS M A, GIACOMINI I, PRAYER-GALETTI T, *et al*. Metabolic plasticity in chemotherapy resistance[J/OL]. Front Oncol, 2020, 10: 281[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7068907/. DOI: 10.3389/fonc.2020.00281.

[34] ZHANG X Y, ZHANG M, CONG Q, *et al*. Hexokinase 2 confers resistance to cisplatin in ovarian cancer cells by enhancing cisplatin-induced autophagy[J/OL]. Int J Biochem Cell Biol, 2018, 95: 9-16 [2023-11-05]. https://www.sciencedirect.com/science/article/abs/pii/S1357272517303163? via% 3Dihub. DOI: 10.1016/j. biocel. 2017. 12.010.

[35] HAN C Y, PATTEN D A, KIM S I, *et al*. Nuclear HKII-P-p53 (Ser15) interaction is a prognostic biomarker for chemoresponsiveness and glycolytic regulation in epithelial ovarian cancer[J/OL]. Cancers, 2021, 13(14): 3399[2023-11-05].https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8306240/.DOI:10.3390/cancers13143399.

[36] PATRA K C, WANG Q, BHASKAR P T, *et al*. Hexokinase 2 is required for tumor initiation and maintenance and its systemic deletion is therapeutic in mouse models of cancer[J]. Cancer Cell, 2013, 24(2): 213-228. DOI: 10.1016/j.ccr.2013.06.014.

[37] YANG H L, SHU Z, JIANG Y Y, *et al*. 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase-2 regulates TP53-dependent paclitaxel sensitivity in ovarian and breast cancers[J]. Clin Cancer Res, 2019, 25(18): 5702-5716. DOI: 10.1158/1078-0432.Ccr-18-3448.

[38] IANG Y X, SIU M K Y, WANG J J, *et al*. PFKFB3 regulates chemoresistance, metastasis and stemness *via* IAP proteins and the NF- κB signaling pathway in ovarian cancer[J/OL]. Front Oncol, 2022, 12: 748403[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8837381/. DOI: 10.3389/fonc.2022. 748403.

[39] CHAO T K, HUANG T S, LIAO Y P, *et al*. Pyruvate kinase M2 is a poor prognostic marker of and a therapeutic target in ovarian cancer [J/OL]. PLoS One, 2017, 12(7): e0182166[2023-11-05]. https://www. ncbi.nlm.nih.gov/pmc/articles/PMC5533430/. DOI: 10.1371/journal.pone.0182166.

[40] ZHOU S C, LI D, XIAO D, *et al*. Inhibition of PKM2 enhances sensitivity of olaparib to ovarian cancer cells and induces DNA damage[J]. Int J Biol Sci, 2022, 18(4): 1555-1568. DOI: 10.7150/ijbs.62947.

[41] TALEKAR M, OUYANG Q, GOLDBERG M S, *et al*. Cosilencing of PKM-2 and MDR-1 sensitizes multidrug-resistant ovarian cancer cells to paclitaxel in a murine model of ovarian cancer[J]. Mol Cancer Ther, 2015, 14(7): 1521-1531. DOI: 10.1158/1535-7163.Mct-15-0100.

[42] ZHANG M, CONG Q, ZHANG X Y, *et al*. Pyruvate dehydrogenase kinase 1 contributes to cisplatin resistance of ovarian cancer through EGFR activation[J]. J Cell Physiol, 2019, 234(5): 6361-6370. DOI: 10.1002/ jcp.27369.

[43] WANG J H, QIAN Y, GAO M Y. Overexpression of PDK4 is associated with cell proliferation, drug resistance and poor prognosis in ovarian cancer[J/OL]. Cancer Manag Res, 2019, 11: 251-262[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC6307676/. DOI: 10.2147/cmar.S185015.

[44] KITAMURA S, YAMAGUCHI K, MURAKAMI R, *et al*. PDK2 leads to cisplatin resistance through suppression of mitochondrial function in ovarian clear cell carcinoma[J]. Cancer Sci, 2021, 112 (11): 4627-4640. DOI: 10.1111/cas.15125.

[45] VENTUROLI C, PIGA I, CURTARELLO M, *et al*. Genetic perturbation of pyruvate dehydrogenase kinase 1 modulates growth,

angiogenesis and metabolic pathways in ovarian cancer xenografts [J/OL]. Cells, 2021, 10(2): 325[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7915933/. DOI: 10.3390/ cells 10020325.

[46] ZHANG W J, SU J, XU H D, *et al*. Dicumarol inhibits PDK1 and targets multiple malignant behaviors of ovarian cancer cells[J/OL]. PLoS One, 2017, 12(6): e0179672[2023-11-05]. https://www.ncbi.nlm.nih. gov/pmc/articles/PMC5472302/. DOI: 10.1371/journal. pone. 0179672.

[47] SHE W Y, LIU T T, LI H M, *et al*. Reprogramming energy metabolism with synthesized PDK inhibitors based on dichloroacetate derivatives and targeted delivery systems for enhanced cancer therapy[J]. J Med Chem, 2023,66(21): 14683-14699. DOI: 10.1021/acs.jmedchem.3c01197.

[48] IKEDA A, YAMAGUCHI K, YAMAKAGE H, *et al*. Serum lactate dehydrogenase is a possible predictor of platinum resistance in ovarian cancer[J]. Obstet Gynecol Sci, 2020, 63(6): 709-718. DOI: 10.5468/ogs.20117.

[49] NONOMIYA Y, NOGUCHI K, KATAYAMA K, *et al*. Novel pharmacological effects of poly(ADP-ribose) polymerase inhibitor rucaparib on the lactate dehydrogenase pathway[J]. Biochem Biophys Res Commun, 2019, 510(4): 501-507. DOI: 10.1016/j.bbrc.2019.01.133.

[50] XIANG J D, ZHOU L N, HE Y Y, *et al*. LDH-a inhibitors as remedies to enhance the anticancer effects of PARP inhibitors in ovarian cancer cells[J]. Aging, 2021, 13(24): 25920-25930. DOI: 10.18632/aging.203780.

[51] WANG C X, YU C X, CHANG H K, *et al*. Glucose-6-phosphate dehydrogenase: a therapeutic target for ovarian cancer[J]. Expert Opin Ther Targets, 2023, 27(8): 733-743. DOI: 10.1080/14728222.2023.2247558.

[52] CATANZARO D, GAUDE E, ORSO G, *et al*. Inhibition of glucose-6-phosphate dehydrogenase sensitizes cisplatin-resistant cells to death[J]. Oncotarget, 2015, 6(30): 30102-30114. DOI: 10.18632/oncotarget.4945.

[53] CATANZARO D, NICOLOSI S, COCETTA V, *et al*. Cisplatin liposome and 6-amino nicotinamide combination to overcome drug resistance in ovarian cancer cells[J]. Oncotarget, 2018, 9(24): 16847-16860. DOI: 10.18632/oncotarget.24708.

[54] YAMAWAKI K, MORI Y, SAKAI H, *et al*. Integrative analyses of gene expression and chemosensitivity of patient-derived ovarian cancer spheroids link G6PD-driven redox metabolism to cisplatin chemoresistance[J/OL]. Cancer Lett, 2021, 521: 29-38[2023-11-05]. https://www.sciencedirect.com/science/article/pii/S0304383521004079?via%3Dihub. DOI: 10.1016/j.canlet.2021.08.018.

[55] SHENG H, FENG Q, QUAN Q, *et al*. Inhibition of stat3 reverses taxol-resistance in ovarian cancer by down-regulating g6pd expression *in vitro*[J]. Biochem Biophys Res Commun, 2022, 617 (Pt 2): 62-68. DOI: 10.1016/j.bbrc.2022.05.091.

[56] FENG Q, LI X, SUN W, *et al*. Targeting G6PD reverses paclitaxel resistance in ovarian cancer by suppressing GSTP1[J/OL]. Biochem Pharmacol, 2020, 178: 114092[2023-11-05]. https://www.sciencedirect.com/science/article/abs/pii/S0006295220303282?via%3Dihub. DOI: 10.1016/j.bcp.2020.114092.

[57] WU Y, ZHANG X, WANG Z, *et al*. Targeting oxidative phosphorylation as an approach for the treatment of ovarian cancer[J/OL]. Front Oncol, 2022, 12: 971479[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9486401/. DOI: 10.3389/fonc.2022.971479.

[58] GENTRIC G, KIEFFER Y, MIEULET V, *et al*. PML-regulated mitochondrial metabolism enhances chemosensitivity in human ovarian cancers[J/OL]. Cell Metab, 2019, 29(1): 156-173. e110 [2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC6331342/. DOI: 10.1016/j.cmet.2018.09.002.

[59] YANG C, ZHAO N N, LI D D, *et al*. Metformin improves the sensitivity of ovarian cancer cells to chemotherapeutic agents[J]. Oncol Lett, 2019, 18(3): 2404-2411. DOI: 10.3892/ol.2019.10564.

[60] TYAGI K, MANDAL S, ROY A. Recent advancements in therapeutic targeting of the Warburg effect in refractory ovarian cancer: a promise towards disease remission[J/OL]. Biochim Biophys Acta Rev Cancer, 2021, 1876(1): 188563[2023-11-05]. https://www.sciencedirect.com/science/article/abs/pii/S0304419X21000603?Via%3Dihub. DOI: 10.1016/j.bbcan.2021.188563.

[61] MA Y B, WANG W, IDOWU M O, *et al*. Ovarian cancer relies on glucose transporter 1 to fuel glycolysis and growth: anti-tumor activity of BAY-876[J/OL]. Cancers, 2018, 11(1): 33[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6356953/. DOI: 10.3390/cancers11010033.

[62] KARAGEORGIS G, RECKZEH E S, CEBALLOS J, *et al*. Chromopynones are pseudo natural product glucose uptake inhibitors targeting glucose transporters GLUT-1 and -3[J]. Nat Chem, 2018, 10(11): 1103-1111. DOI: 10.1038/s41557-018-0132-6.

[63] RECKZEH E S, WALDMANN H. Small-molecule inhibition of glucose transporters GLUT-1-4[J]. Chembiochem, 2020, 21(1-2): 45-52. DOI: 10.1002/cbic.201900544.

[64] CHAN D W, YUNG M M, CHAN Y S, *et al*. Map30 protein from momordica charantia is therapeutic and has synergic activity with cisplatin against ovarian cancer *in vivo* by altering metabolism and inducing ferroptosis[J/OL]. Pharmacol Res, 2020, 161: 105157 [2023-11-05]. https://www. sciencedirect. com/science/article/pii/S1043661820314651?via%3Dihub. DOI: 10.1016/j.phrs.2020.105157.

[65] ZHANG L L, SU J, XIE Q, *et al*. 2-deoxy-d-glucose sensitizes human ovarian cancer cells to cisplatin by increasing ER stress and decreasing ATP stores in acidic vesicles[J]. J Biochem Mol Toxicol, 2015, 29(12): 572-578. DOI: 10.1002/jbt.21730.

[66] MONDAL S, ROY D, SARKAR BHATTACHARYA S, *et al*. Therapeutic targeting of PFKFB3 with a novel glycolytic inhibitor POFK158 promotes lipophagy and chemosensitivity in gynecologic cancers[J]. Int J Cancer, 2019, 144(1): 178-189. DOI: 10.1002/ijc.31868.

[67] QIU X T, LI Y, ZHANG Z Y. Crosstalk between oxidative phosphorylation and immune escape in cancer: a new concept of therapeutic targets selection[J]. Cell Oncol, 2023, 46(4): 847-865. DOI: 10.1007/s13402-023-00801-0.

[68] KAPUR A, MEHTA P, SIMMONS A D, *et al*. Atovaquone: an inhibitor of oxidative phosphorylation as studied in gynecologic cancers[J/OL]. Cancers (Basel), 2022, 14(9): 2297[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9102822/. DOI: 10.3390/cancers14092297.

[69] GUO Y, HU B, FU B B, *et al*. Atovaquone at clinically relevant concentration overcomes chemoresistance in ovarian cancer *via* inhibiting mitochondrial respiration[J/OL]. Pathol Res Pract, 2021, 224: 153529 [2023-11-05]. https://www.sciencedirect.com/science/

article/abs/pii/S0344033821001904? via% 3Dihub. DOI: 10.1016/j.prp.2021.153529.

[70] TANG S S, SHEN Y, WEI X, *et al*. Olaparib synergizes with arsenic trioxide by promoting apoptosis and ferroptosis in platinum-resistant ovarian cancer[J/OL]. Cell Death Dis, 2022, 13(9): 826[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC9513087/. DOI: 10.1038/s41419-022-05257-y.

[71] DEWAAL D, NOGUEIRA V, TERRY A R, *et al*. Hexokinase-2 depletion inhibits glycolysis and induces oxidative phosphorylation in hepatocellular carcinoma and sensitizes to metformin[J/OL]. Nat Commun, 2018, 9(1): 446[2023-11-05]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5792493/. DOI: 10.1038/ s41467-017-02733-4.

[72] AHAMED A, HOSEA R, WU S, *et al*. The emerging roles of the metabolic regulator g6pd in human cancers[J/OL]. Int J Mol Sci, 2023, 24(24): 17238[2023-11-05]. https://www. ncbi. nlm. nih. gov/pmc/articles/ PMC10743588/. DOI: 10.3390/ijms242417238.

[73] GHILARDI C, MOREIRA-BARBOSA C, BRUNELLI L, *et al*. PGC1α/β expression predicts therapeutic response to oxidative phosphorylation inhibition in ovarian cancer[J]. Cancer Res, 2022, 82(7): 1423-1434. DOI: 10.1158/0008-5472.Can-21-1223.

[74] MARCUCCI F, RUMIO C. Glycolysis-induced drug resistance in tumors-a response to danger signals? [J]. Neoplasia, 2021, 23(2): 234-245. DOI: 10.1016/j.neo.2020.12.009.

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