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综述

靶向肾透明细胞癌糖代谢重编程药物的研究进展

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摘要：肾透明细胞癌(clear cell renal cell carcinoma，ccRCC)是肾癌的最常见类型。近年来，靶向和免疫治疗对于转移性ccRCC的治疗取得了重要进展，但总体预后仍然较差。ccRCC的发生发展以其独特的代谢改变为显著特点，表现为有氧糖酵解(aerobic glycolysis)、磷酸戊糖途径(pentose phosphate pathway，PPP)、脂肪酸合成(fatty acid synthesis)、谷氨酰胺(glutamine)和谷胱甘肽(glutathione)代谢的上调，以及三羧酸循环(tricarboxylic acid cycle，TCA cycle)、脂肪酸β氧化(fatty acid β-oxidation，FAO)和氧化磷酸化(oxidative phosphorylation，OXPHOS)的下调。这些代谢特征的改变被概括为“代谢重编程”。本文仅以ccRCC中糖代谢重编程为重点，综述ccRCC中糖代谢的变化，以及针对该过程的关键酶及转运体的药物开发，探讨针对ccRCC“糖代谢重编程”进行靶向治疗的意义和研究现状，为ccRCC的治疗提供新思路。

关键词：肾透明细胞癌；糖代谢；代谢重编程；靶向治疗

Research progress on glucose metabolism reprogramming drugs targeting renal clear cell carcinoma

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Abstract: Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer. In recent years, targeted and immunotherapy have made important progress in the treatment of metastatic ccRCC, but the overall prognosis remains poor. Clear cell renal cell carcinoma is characterized by unique metabolic alterations, including upregulation of aerobic glycolysis, the pentose phosphate pathway (PPP), fatty acid synthesis, glutamine and glutathione metabolism, and downregulation of the tricarboxylic acid cycle (TCA cycle), fatty acid β-oxidation (FAO) and oxidative phosphorylation (OXPHOS). These metabolic changes are summarized as “metabolic reprogramming”. This review focuses on the reprogramming of glucose metabolism

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in ccRCC, summarizing the alterations in glucose metabolism and the development of inhibitors targeting key enzymes and transporters involved in this process, and providing new strategies for the treatment of ccRCC.
Key Words：clear cell renal cell carcinoma; glucose metabolism; metabolic reprogramming; targeting therapy

肾透明细胞癌(clear cell renal cell carcinoma，ccRCC)是肾癌中最常见的类型，占所有肾癌的80%[1]。ccRCC被认为是一种代谢相关疾病，参与代谢途径的相关基因在ccRCC中常存在多种突变。脂质和糖原代谢的改变导致ccRCC形成嗜伊红的透明细胞质，这也是ccRCC重要的形态学特征之一[2]。ccRCC的转录组、蛋白质组和代谢组分析均支持代谢途径相关基因和蛋白质参与了ccRCC的发生发展，揭示了ccRCC存在有氧糖酵解(aerobic glycolysis)、磷酸戊糖途径(pentose phosphate pathway，PPP)、脂肪酸合成(fatty acid Synthesis)、谷氨酰胺(glutamine)和谷胱甘肽(glutathione)等代谢途径及其产物的上调，以及三羧酸循环(tricarboxylic acid cycle，TCA cycle)、脂肪酸β氧化(fatty acid β-oxidation，FAO)和氧化磷酸化(oxidative phosphorylation，OXPHOS)等代谢途径及其产物的下调[3-5]。ccRCC中存在的这些代谢变化通常被称为“代谢重编程”。“代谢重编程”是ccRCC的关键分子病理特征之一，深入研究“代谢重编程”有助于我们进一步理解ccRCC的发生发展机制和开发新的有效治疗药物。本文拟针对ccRCC中糖代谢的“重编程”研究进展进行综述，阐述ccRCC糖代谢的特点，并简介目前针对转移性ccRCC糖代谢重编程的药物研发进展。

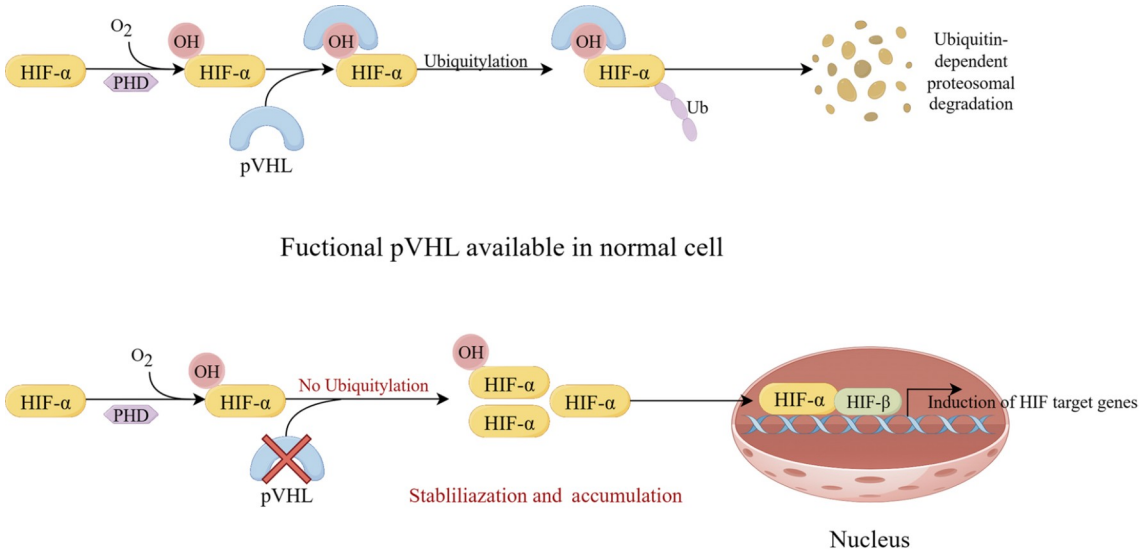
1 ccRCC代谢的特点

在有氧条件下，正常细胞利用葡萄糖进行糖酵解生成丙酮酸，丙酮酸在丙酮酸脱氢酶复合体(pyruvate dehydrogenase complex，PDH complex，PDC)的催化下变成乙酰辅酶A(acetyl-coA)并进入三羧酸循环。这一完整的氧化过程可以在随后的氧化磷酸化过程中为细胞带来最多的腺嘌呤核苷三磷酸(adenosine-triphosphate triphosphate，ATP)并为细胞提供充分的能量。即使在缺氧的条件下，细胞的感受器也可以感知低氧环境并做出一系列适应性的改变，如红细胞和血管的生成增加、糖代谢限速酶的表达和活性上调，从而使细胞避免通过糖酵解这种低效的方式获取能量，而是尽可能通过三羧酸循环来获得能量来源。然而肿瘤细胞与正常细胞不同，即使在氧气充足的条件下也选择采用糖酵解的方式供能，这被称为Warburg效应(Warburg effect)，又叫做“有氧糖酵解”[6]。Warburg效应帮助肿瘤在缺乏血供和氧气的情况下快速生长和扩散，并且有利于提升肿瘤细胞对细胞凋亡和免疫系统破坏的抵抗力[7]。

正常细胞和肿瘤细胞对于缺氧环境的不同反应主要受到缺氧诱导因子(hypoxia-inducible factor，HIF)家族的调控，尤其是HIF-1α和HIF-2α[8]。HIF-1α和HIF-2α是*VHL*(von Hippel-Lindau)基因编码的von Hippel-Lindau蛋白(pVHL)的主要底物。HIF-1α和HIF-2α含有脯氨酸残基氧依赖性降解结构域(oxygen-dependent degradation domains，ODDDs)，并以此结构域与pVHL相互作用。在常氧状态下，这些脯氨酸残基被铁和氧依赖的脯氨酸羟基化酶(prolyl hydroxylase-domain protein，PHD)羟基化，使得HIF蛋白通过pVHL介导并泛素化，随后经蛋白酶体途径降解。常氧状态下，由于大量的HIF被蛋白酶体水解，HIF-1α保持在低水平。当氧气不足时，HIF-1α无法被羟化，大量未被羟基化的HIF-1α浓度持续升高，与其专性伴侣蛋白HIF-1β形成异二聚体，并且执行它作为转录因子的功能[9]。ccRCC由于常发生*VHL*基因的失活或突变，使得HIF不能与pVHL相互结合，不能经pVHL途径被泛素化及经蛋白酶体水解[10]，从而形成“假性缺氧”环境，导致HIF不断堆积。HIF的不断堆积在肿瘤的发生发展中起到重要的促进作用，包括糖酵解增加、促进肿瘤血管生成、促进肿瘤侵袭与转移等[11,12]，如图1所示。

2 ccRCC中糖代谢重编程的关键靶点

在ccRCC中，糖代谢重编程体现在某些关键代谢过程蛋白质的改变上。研究揭示了多种蛋白质



氧气充足时HIF-α可在PHD的催化下被羟基化。正常的细胞中存在的pVHL可与羟基化的HIF-α结合使其泛素化而被降解。但在ccRCC细胞中由于pVHL的缺失，羟基化的HIF-α无法经泛素化途径降解，导致其不断积累，进入细胞核内促进缺氧相关基因的转录。HIF-α：缺氧诱导因子-α(hypoxia-inducible factor-α)；PHD：脯氨酸羟基化酶(prolyl hydroxylase-domain protein)；Ub：泛素(ubiquitin)；ccRCC：肾透明细胞癌(clear cell renal cell carcinoma)；HIF-β：缺氧诱导因子-β(hypoxia-inducible factor-β)

图1　pVHL对HIF-α的调节作用

在这些关键环节中的表达上调，这些蛋白质在糖代谢中起着至关重要的作用。这一发现阐释了ccRCC改变代谢的具体机制。同时，这些表达上调的蛋白质也为针对ccRCC的靶向治疗策略提供了有力的科学依据。

2.1　葡萄糖转运相关膜蛋白

葡萄糖转运体属于溶质载体超家族(solute carriers family，SLC)，主要包括两类：葡萄糖转运蛋白(glucose transporters，GLUT)和钠依赖的葡萄糖共转运体(sodium-glucose cotransporter，SGLT)。这些蛋白质位于细胞膜上，在细胞膜内与膜外的葡萄糖转运中发挥重要作用。其中，GLUT通过细胞膜内外的葡萄糖浓度梯度进行异化扩散，而SGLT则通过钠的电化学梯度来转运葡萄糖[13]。葡萄糖的转运是肿瘤细胞利用葡萄糖的第一步。由于Warburg效应，肿瘤细胞即使在常氧状态下也更多地选择糖酵解供能，与糖酵解相关的所有酶几乎均有表达增加[4,14]，这种方式较正常细胞的三羧酸循环产生更少的ATP，并且肿瘤细胞生长活跃对于ATP的需求更高，加上丙酮酸脱氢酶受到升高的HIF的抑制使进入三羧酸循环的葡萄糖减少[15]，因此肿瘤细胞有必要摄取并消耗更多的葡萄糖以满足自身所需，在ccRCC肿瘤细胞，葡萄糖的转运也随之显著上调[16]。

2.1.1　GLUT

GLUT是一类膜蛋白，介导了肿瘤细胞利用葡萄糖的第一步。在肾癌细胞中，由于HIF-1α的不断积累，GLUT1的表达较正常肾组织明显升高[17]，从而促进肿瘤细胞对葡萄糖的摄取。肿瘤细胞的GLUT1高表达能促进肿瘤的进展[18]，葡萄糖剥夺或阻断GLUT1的活性可抑制ccRCC细胞的增殖并促进其凋亡[19]。临床研究发现，ccRCC患者肿瘤细胞内GLUT1的表达水平与其Fuhrman分级正相关，高水平的GLUT1表达往往提示较差的预后[20]。此外，肿瘤细胞高表达的GLUT1往往伴随CD8阳性T细胞浸润的减少，表明GLUT1可能在肾癌免疫逃逸机制中发挥作用[21]。GLUT1在ccRCC的发生发展过程中发挥着重要的作用，限制肿瘤细胞GLUT1的功能或许可以成为ccRCC治疗的新靶点。

2.1.2　SGLT

SGLT在人体中主要分为两种类型：SGLT1和SGLT2。SGLT1主要存在于肠道上皮细胞中，负责

将葡萄糖从肠道吸收进入血液。SGLT2则主要存在于肾小管上皮细胞中，负责将通过肾小球滤过的葡萄糖重吸收回血液，减少葡萄糖的丢失。此外，SGLT2在小肠、胰腺以及包括肾细胞癌在内的多数肿瘤中都有表达升高，如前列腺、肺癌、胰腺癌等[22-24]。与GLUT相似，肿瘤细胞也可通过上调的SGLT增强对葡萄糖的摄取，而SGLT2的抑制可抑制肿瘤细胞的增殖并促进其凋亡[25]。有研究发现，SGLT2在肾癌组织中的表达与预后相关[26]，目前针对SGLT2的相关研究较少，加强对SGLT2的研究可能有助于对肾癌代谢特点的理解。

2.2 有氧糖酵解途径相关代谢酶

葡萄糖由葡萄糖转运蛋白转运至细胞内后，需要经过一系列代谢酶的处理，转变为ATP并给细胞供能。在正常细胞中，转运至细胞内的葡萄糖会进一步进入线粒体，并通过三羧酸循环将葡萄糖转变为ATP供能，而ccRCC细胞则由于代谢途径一系列酶的改变，使这些细胞内的葡萄糖并不进入线粒体，而是在细胞质内通过糖酵解途径获取ATP。

2.2.1 己糖激酶(hexokinase，HK)

HK是糖代谢的第一个限速酶，能将葡萄糖转化为葡萄糖-6-磷酸。HK1在大多数哺乳动物成年组织中表达，HK2仅在少数成年组织中高水平表达，如脂肪、骨骼和心肌[27]。肿瘤细胞常伴有HK2的表达增加，在ccRCC中HK2的表达增加较正常肾组织尤为突出[28]，这是由于ccRCC中过量的HIF-1α转录上调了HK2的表达[29]。HK的高表达往往与肿瘤的耐药性和转移能力成正相关，体外诱导HK2的表达可增强肿瘤的侵袭性和增殖[30,31]，提示HK2可作为潜在的治疗靶点。

2.2.2 磷酸果糖激酶(phosphofructokinase，PFK)

PFK是糖酵解途径的第二个限速酶，催化果糖-6磷酸转化为果糖-1,6-二磷酸。PFK存在三种亚型——PFKL、PFKM和PFKP[32]。PFK的活性受代谢产物的影响，果糖-2,6-二磷酸是其最强的别构激活剂。而果糖-2,6-二磷酸由果糖-2,6-二磷酸酶(6-phosphofructo-2-kinase/fructose-2,6-biphosphatase，PFKFB)磷酸化果糖-6-磷酸产生[33]。由于PFKFB可以调控细胞内磷酸果糖的浓度，从而调节PFK的活性，影响糖酵解和糖原合成等代谢途径。其中，PFKFB3是最常见的亚型，并且在包括ccRCC在内的多种肿瘤中发现其过度表达，其高表达往往预示患者较晚期的TNM分期和较差的预后[34]。*PFKFB3*的敲低能够抑制ccRCC细胞的糖酵解、增殖并阻断其细胞周期G_1/S转化[35]。另外，ccRCC中也常伴有PFKFB4的过表达，有研究发现敲低ccRCC中的PFKFB4的表达可抑制其增殖和侵袭能力，并增强肿瘤细胞对舒尼替尼的敏感性[36]。因此，PFKFB是ccRCC代谢治疗中的一个潜在靶点。

2.2.3 丙酮酸激酶(pyruvate kinase，PK)

丙酮酸激酶是糖酵解途径的最后一个关键酶，它催化磷酸烯醇式丙酮酸(phosphoenolpyruvate，PEP)转化为ATP和丙酮酸，在哺乳动物中存在4种PK亚型(PKL、PKR、PKM1、PKM2)。其中，PKM2在胚胎组织、干细胞、肿瘤细胞等快速增殖细胞中表达[37]。PKM2有二聚体和四聚体两种形式，正常细胞中主要为四聚体，肿瘤细胞中主要为二聚体[37,38]。低活性的二聚体PKM2限制PEP转变为丙酮酸，这导致大量的糖酵解中间产物进入旁路途径，为肿瘤的增殖提供了大量的原料[39]。有研究发现，通过激活PKM2向四聚体的转化可逆转肿瘤细胞的有氧糖酵解，减少糖酵解中间产物的合成，继而抑制肿瘤合成代谢，阻碍肿瘤的生长[40,41]。二聚体形式的PKM2通过磷酸化AKT1S1而激活哺乳动物雷帕霉素复合体1(mammalian target of rapamycin complex 1，mTORC1)。因此，PKM2的过表达不仅促进产生大量中间产物用于生物合成，还能激活哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)信号传导，促进这些中间产物进行合成代谢，促进肿瘤生长[42,43]。鉴于PKM2在ccRCC组织中的过度表达及其参与PI3K/AKT/mTOR的蛋白激酶活性，靶向PKM2可能是抑制肾癌合成代谢和抑制疾病进展的一种手段。

2.2.4 丙酮酸脱氢酶复合体

PDC是一种生物体内催化丙酮酸转变成乙酰辅酶A的复合酶。它由三种酶[丙酮酸脱氢酶(pyruvate dehydrogenase，PDH)、二氢硫辛酰转乙酰基酶、二氢硫辛酸脱氢酶]和六种辅助因子(焦磷酸硫胺素、硫辛酸、黄素腺嘌呤二核苷酸、烟酰胺腺嘌呤二核苷酸、辅酶A和Mg离子)组成。丙酮酸脱氢

酶是这个复合体中的关键酶之一，它负责将丙酮酸转化为乙酰辅酶A，后者将进入三羧酸循环进行进一步的代谢。PDH的活性可由丙酮酸脱氢酶激酶(pyruvate dehydrogenase kinases，PDKs)和丙酮酸脱氢酶磷酸酶(pyruvate dehydrogenase phosphatases，PDPs)共同调控。PDK主要有三种亚型，PDK1、PDK2和PDK3。HIF-1α可直接反式激活编码PDK1的基因使其表达显著增加[44]。PDK1表达增加使PDH大量失活，这将丙酮酸从三羧酸循环中分流，导致乳酸的大量生成。由于*VHL*基因的失活导致的HIF-1α在肾癌细胞中的大量堆积，PDK1在肾癌组织中的表达较周围正常肾组织明显升高[45]，提示抑制PDK可能有助于ccRCC的治疗。

2.3 乳酸生成和转运途径相关蛋白

伴随糖酵解的发生，一方面，ccRCC细胞低效获得了ATP，获得了自身生长浸润迁移的能量来源；另一方面，细胞内产生了大量乳酸。这些过量的乳酸将导致细胞内稳态的改变。因此，肿瘤细胞会将过量产生的乳酸转运至细胞外，从而维持自身内环境的稳定。乳酸在ccRCC细胞的大量生成与排泄，也是ccRCC细胞代谢重编程的特点之一。

2.3.1 乳酸脱氢酶(lactate dehydrogenase，LDH)

乳酸脱氢酶能催化丙酮酸和乳酸之间的氧化还原反应，在人体内有五种亚型，受到HIF-1和c-Myc的调节[46]。葡萄糖进入三羧酸循环减少而糖酵解处于高度活跃状态，这一过程使丙酮酸不断堆积，同时HIF-1α上调LDHA的表达，促进丙酮酸转化为乳酸[47]。ccRCC组织中LDHA表达较正常肾组织显著升高，且LDHA的表达与患者的无病生存期和总体生存率显著负相关[48]。研究表明，LDHA的表达增加将增强肿瘤细胞的生长和迁移能力[18]。而下调LDHA表达能抑制肿瘤细胞的生长[49]，同时肿瘤的侵袭和免疫逃逸能力显著下降[2]。靶向LDHA、抑制丙酮酸向乳酸的转变可能成为ccRCC治疗的新靶点。

2.3.2 单羧酸转运蛋白(monocarboxylate transporters，MCTs)

乳酸在肿瘤细胞内不断堆积，而编码乳酸转运蛋白的基因，如*MCT1*和*MCT4*在肿瘤细胞中上调[50]，这使得大量的乳酸被转移至细胞外。细胞外大量的乳酸可能阻碍$CD8^+$ T细胞的增殖和活化，这为肿瘤细胞的免疫逃逸提供了帮助[51]。同时，酸化的肿瘤微环境促进血管内皮生长因子(vascular endothelial growth factor，VEGF)的分泌和血管生成[52,53]，有利于肿瘤的发生发展。在肾癌患者中高表达的MCTs与较差的预后和较短的生存期相关[54,55]，MCT1和MCT4的表达增加增强了肾透明细胞癌的增殖和侵袭能力[56]，阻断MCTs可降低肿瘤细胞外的乳酸水平，削弱肿瘤细胞的增殖和侵袭能力，抑制肿瘤内血管生长[55]。开发新的MCT靶向疗法或将为ccRCC的治疗提供新的希望[57]。

3 靶向ccRCC糖代谢重编程的治疗

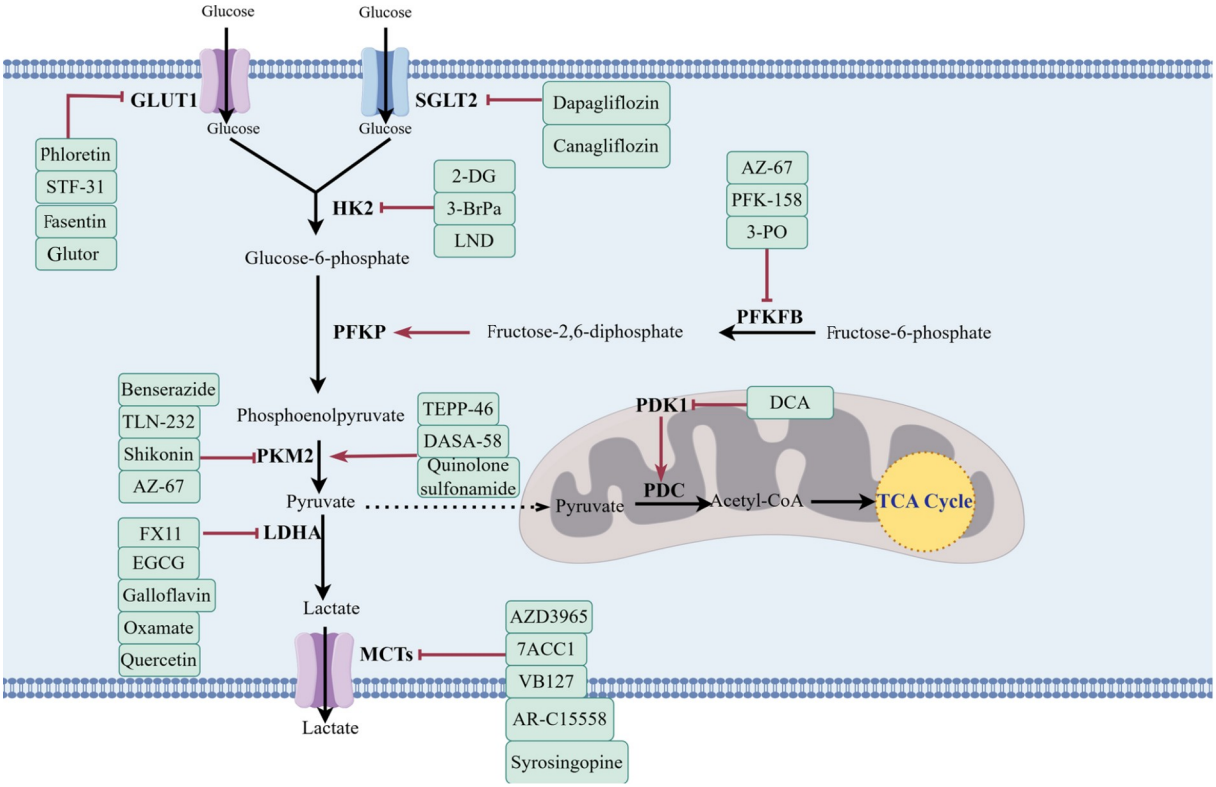
随着对ccRCC中糖代谢重编程认识的深入，目前认为糖代谢重编程中的一些关键酶和转运蛋白有可能成为未来治疗ccRCC的潜在靶点，目前正针对这些新的靶点在研发一系列药物，如图2所示。以下简述靶向ccRCC糖代谢重编程的药物研究进展。

3.1 靶向葡萄糖转运

由于Warburg效应，ccRCC细胞的能量产生效率显著低于正常细胞[6]。ccRCC作为一种代谢和生长旺盛的肿瘤，对葡萄糖的需求量异常巨大。为了满足其快速增长和高代谢活性，ccRCC细胞必需大幅增加对葡萄糖的摄取。这种对葡萄糖的过量需求导致了对GLUT和SGLT表达水平的上调，这些转运蛋白在ccRCC细胞中的高表达成为了其与正常细胞之间的一个显著差异[16]。因此，通过对这些转运蛋白进行干预，可以有效遏制ccRCC肿瘤细胞的生长，为治疗提供了新的策略。

3.1.1 靶向GLUT

多种小分子可以选择性地抑制GLUT，包括多种天然提取物(生物碱、黄酮类化合物)和其他氧杂环化合物及酚类化合物[58]。其中，根皮素(phloretin)[59]、染料木素(genistein)[60]、姜黄素(curcumin)[61]、槲皮素(quercetin)[62]等25种天然提取物在肿瘤模型中表现出抗癌作用。多酚是一类天然的GLUT抑制剂，有实验表明，其能抑制癌细胞对葡萄糖的摄取，进而抑制癌细胞的增殖[63,64]。GLUT抑制剂染料木素可通过增加CDKN2a的表达，并降低CDKN2a的甲基化而诱导肾癌细胞凋亡[65]，



该图展示了ccRCC的“糖代谢重编程”过程，并列举了本文中提及的部分靶向“糖代谢重编程”的药物及其作用位点。GLUT：葡萄糖转运蛋白(glucose transporters)；SGLT：钠-葡萄糖共转运体(sodium-glucose co-transporter)；HK2：己糖激酶2(hexokinase 2)；PFKP：血小板型磷酸果糖激酶(the platelet isoform of phosphofructokinase)；PFKFB：果糖-2,6-二磷酸酶(6-phosphofructo-2-kinase/fructose-2,6-biphosphatase)；LDHA：乳酸脱氢酶A(lactate dehydrogenase A)；PKM2：丙酮酸激酶M2(pyruvate kinase M2)；MCTs：单羧酸转运蛋白(monocarboxylate transporters)；PDC：丙酮酸脱氢酶复合体(pyruvate dehydrogenase complex，PDH complex)；PDK1：丙酮酸脱氢酶激酶1(pyruvate dehydrogenase kinase 1)；TCA：三羧酸循环(tricarboxylic acid cycle)；MCTs：单羧酸转运蛋白(monocarboxylate transporters)

图2 靶向ccRCC“糖代谢重编程”的药物

并能通过下调miR-1260b的表达进而影响Wnt信号通路来抑制肾癌组织的生长和转移[66]。此外，还有一些人工合成的小分子GLUT抑制剂，在临床前模型中通过抑制肿瘤细胞的葡萄糖摄取证明了其抗癌作用。如WZB117是一种多酚衍生的GLUT小分子抑制剂，可减少肿瘤细胞内GLUT1的表达并降低糖酵解的活性，进而抑制肿瘤细胞的能量供应，发挥抗肿瘤作用[67]。但其在水溶液中的不稳定性极大限制了其临床应用[67]。与WZB117相比，新型GLUT抑制剂DRB18具有更好的稳定性[68]，并且在多种肿瘤细胞系中表现出更明显的抑制葡萄糖摄取的能力，提示其在抗肿瘤领域具有更好的前景[69]。STF-31能靶向GLUT1，抑制ccRCC细胞及其他糖酵解活跃的肿瘤细胞对葡萄糖的摄取并抑制其生长[19]。并且由于正常的肾细胞并不严格依赖于糖酵解和GLUT1转运葡萄糖，其对STF-31的毒性不敏感[19]。但人体内多种正常组织都表达GLUT1，特别是红细胞表面只有GLUT1的表达[70]，这为STF-31的临床应用造成了限制。Fasentin可与GLUT1和GLUT4结合抑制肿瘤细胞摄取葡萄糖[71]。近年来有研究发现，它可以抑制内皮细胞的增殖，因此可能具有抗血管生成治疗策略的意义[72]，但其安全性需要进一步验证。谷蛋白(glutor)是一种新型的GLUT抑制剂，能同时靶向GLUT1、GLUT2和GLUT3，已在多种肿瘤模型中证明其抑癌作用[73]，并且对正常健康组织细胞有较好的安全性[74]。KL-11743可在体外特异性阻断癌细胞的葡萄糖摄取，在多种肿瘤的体外模型中表现出明显的抑制作用，尤其是三羧酸循环缺陷的细胞系中，表现出更为明显的疗效[75]。NV-5440可以同时靶向mTORC1和GLUT1来调节细胞代谢，有效抑制葡萄糖摄取，抑制肿瘤细胞的增殖，并且NV-

5440在体内具有良好的稳定性，这种双靶点代谢抑制剂或许可以在肾癌中发挥更好的治疗效果[76]。

目前尚无GLUT抑制剂用于肾癌的临床试验，但在早期的前列腺癌Ⅰ期临床试验中，GLUT抑制剂带来了显著的不良反应[77]。GLUT抑制剂目前仍存在一些问题，如GLUT在体内分布广泛、其应用易对正常细胞产生影响，并且由于肿瘤细胞的异质性，GLUT不同亚型的表达水平差异可能影响GLUT抑制剂的抗肿瘤效果[78]。GLUT抑制剂的临床应用目前仍有明显的限制，需要进一步探索。

3.1.2 靶向SGLT

SGLT-2抑制剂目前主要获批用于糖尿病患者控制血糖。研究发现，SGLT-2抑制剂可在肝癌、胰腺癌、前列腺癌等多种肿瘤中表现出抑制作用[79]。体外实验证明，达格列净(dapagliflozin)作为SGLT-2抑制剂可以降低肾癌细胞的活力，促进肿瘤细胞凋亡，减小肿瘤体积[22,80]。卡格列净(canagliflozin)可减少肾癌细胞中葡萄糖的内流，抑制Wnt/β-catenin信号通路的激活，降低丙酮酸羧化酶和丙酮酸脱氢酶1的表达，从而抑制肿瘤细胞的糖酵解功能，并抑制肿瘤细胞生长[81,82]。另外，有研究发现，卡格列净可促进AMPK活性，抑制MAPK和mTOR-p70S6k/4EBP1通路，激活细胞周期检查点，并通过部分抑制HIF-1α抑制肿瘤增殖[83]。SGLT-2抑制剂的抗肿瘤作用已在多种肿瘤模型中得到验证，提示其可作为潜在的抗肿瘤药物[84]。SGLT-2抑制剂作为广泛使用的糖尿病药物，其本身的安全性已受到广泛的验证，这是其作为潜在抗肿瘤药物的重大优势，但SGLT-2抑制剂抗肿瘤的具体机制仍存在争议，需要进一步研究。

3.2 靶向糖酵解限速酶

肾癌细胞内的葡萄糖主要通过糖酵解途径进行代谢，这一过程在肿瘤细胞中异常活跃，以满足其不断增长的能量需求。为了应对这种高能消耗，肿瘤细胞不得不提高糖酵解的效率。在此过程中，糖酵解途径中的关键酶的表达水平显著上调，与正常细胞相比，这一特征显得尤为突出[14]。正常细胞通常主要依赖三羧酸循环(TCA循环)来供能，这一代谢途径在能量产生上更为高效。这种代谢差异为肾癌的靶向治疗提供了可能。通过抑制糖酵解途径中的关键酶可以有效阻断肿瘤细胞的能量供应，从而抑制其生长。由于正常细胞更多地依赖于TCA循环，这种针对糖酵解关键酶的治疗策略对正常细胞的影响相对较小，从而降低了治疗过程中的不良反应。因此，靶向肾癌细胞中糖酵解途径的关键酶，不仅有望有效遏制肿瘤的生长，而且可能在保持正常细胞功能的同时，提高治疗的安全性。这一治疗策略在未来的研究和临床试验中具有广阔的应用前景。

3.2.1 靶向HK

葡萄糖类似物2-脱氧-D-葡萄糖(2-deoxy-D-glucose，2-DG)在进入细胞经HK2催化后转化为2-脱氧-D-葡萄糖6-磷酸(2-deoxy-d-glucose-6-phosphate，2-DG-6-P)，将糖酵解阻断于起始阶段[85]。早期研究证明，2-DG的单药治疗在肿瘤治疗中不尽如人意[86]，但它在与其他药物的联用中增加了原有药物的疗效。一项关于2-DG联合酪氨酸激酶抑制剂的体外实验发现，2-DG与酪氨酸激酶抑制剂联合使用降低了ATP的产生，并增加了ccRCC对培唑帕尼治疗的敏感性[85]。WP1112是一种新型2-DG类似物，与2-DG相比表现出更强的抗癌作用，并且在小鼠模型中表现出良好的耐受性，现已进入治疗多型胶质母细胞瘤的Ⅰ期临床试验[87,88]。3-溴丙酮酸(3-bromopyruvate，3-BrPa)是一种高活性的丙酮酸类似物，可作为HK2抑制剂抑制肿瘤细胞糖酵解，导致ATP耗竭而凋亡[89]。体外实验证明，原代ccRCC细胞对3-溴丙酮酸敏感，在正常原代肾细胞耐受的浓度下，可抑制ccRCC细胞糖酵解并诱导其凋亡[90]。目前，有研究将3-溴丙酮酸与纳米材料相结合，增加了肿瘤对放疗及光动力治疗的敏感性，并降低了其不良反应[91,92]。氯尼达明(lonidamine，LND)是一种吲哚衍生物，研究表明，LND作为HK-2抑制剂能够抑制糖酵解[93]。与2-DG相似，单药治疗效果不明显。但联合治疗研究结果表明，氯尼达明可提高多种肿瘤对放化疗的敏感性[94]。有研究将氯尼达明与脂质体(liposomes，LPs)相结合组成纳米药物，通过纳米药物可在肿瘤体内蓄积的特性，增强了氯尼达明的疗效，降低了不良反应[95-97]。BNBZ(Benitrobenrazide)是一种新型HK抑制剂，可与HK2直接结合，显著抑制肿瘤细胞的糖酵解，抑制肿瘤增殖[98]。BNBZ直接靶向HK2，具有高效性和

低毒性，是具有潜力的抗肿瘤药物[98]。此外，目前还发展了多种新型HK2抑制剂，如sinominine[99]、IKA(Ikarugamycin)[100]，这些HK2抑制剂在体外实验中均表现出良好的肿瘤抑制作用，提示HK2抑制剂具有潜在的治疗ccRCC的价值。

3.2.2 靶向PFKFB

研究人员将PFKFB3作为潜在的治疗靶点，开发了针对该酶的抑制剂，以干扰肿瘤细胞的糖代谢，并有望用于肿瘤治疗[101-103]。这些抑制剂可以通过抑制PFKFB3的活性，降低磷酸果糖的水平，从而抑制肿瘤细胞的生长和扩散，如3-PO[104]、PFK-158[105]等。在细胞实验中，3-PO抑制PFKFB3能有效抑制RCC细胞的糖酵解和生长，但3-PO的溶解度差，难以获得足够高的有效浓度以达到治疗效果，且选择性较低，故临床应用受限[106]。PFK158是3-PO的衍生物，与3-PO相比，其选择性及抑制效果都得到了明显的增强[107]，已在2014年被纳入晚期实体恶性肿瘤患者的Ⅰ期临床试验(NCT02044861)，并且在一年的随访期内无严重不良事件的报告，但该试验因药物的有效性较低而被终止[108]。研究发现，新型PFKFB3抑制剂KAN0438757可显著降低结肠癌细胞的迁移和侵袭能力，并抑制肿瘤细胞的侵袭，而对正常组织及健康小鼠无明显的毒性[109]，但其治疗在肾癌中仍需进一步研究。其他新型药物化合物26[110]、PQP[111]等仅在体外实验中证明其抗肿瘤作用，需要在肾癌细胞及移植瘤模型中进一步验证。目前针对PFKBF4的抑制剂较少，化合物5MPN可通过抑制肿瘤细胞的PFKBF4发挥抗肿瘤作用[112]，但随着新的PFKFB抑制剂的研发，或许能为转移性ccRCC患者提供更多治疗选择。

3.2.3 靶向PKM2

TLN-232是一种PKM2抑制剂，目前正在进行转移性RCC患者的Ⅱ期临床试验(NCT00422786)。TLN-232能靶向PKM2，导致糖酵解的终止，起到抑制肿瘤增殖的作用[113]。紫草素(shikonin)也可抑制PKM2并在肾癌的体外试验中证明可抑制肿瘤细胞生长[114,115]，并可通过抑制AKT/mTOR通路增强耐药RCC细胞对舒尼替尼的敏感性[116]。紫草素对于肾癌细胞生长的抑制作用明显，但在不同肾癌细胞系中的抑制作用程度不一，因此需要进一步研究其在不同亚型中的治疗作用[116]。苄丝肼(benserazide，BEN)是一种新型PKM2抑制剂，在黑色素瘤和结肠癌中证明BEN可与PKM2直接结合并阻断PKM2的活性，从而抑制糖酵解，促进肿瘤细胞凋亡，抑制肿瘤生长[117,118]。新型PKM2抑制剂化合物3h可显著抑制肿瘤细胞的糖酵解和线粒体呼吸，导致肿瘤细胞凋亡及自噬死亡[119]。此外，激活PKM2的四聚体形式，恢复其作为丙酮酸激酶的活性，有望逆转Warburg效应，抑制肿瘤的发生发展[39]。研究发现，一系列小白菊内酯(parthenolide，PTL)具有PKM2激活活性，其中衍生物29e对PKM2表现出良好的活性，可促进PKM2二聚体向四聚体的转化，在体外及体内实验中显著抑制肿瘤细胞生长[120]。此外，TEPP-46、Quinolone sulfonamide和DASA-58均可激活PKM2的丙酮酸激酶活性，在动物实验中证明可抑制小鼠肿瘤模型的生长[40,121]。

3.2.4 靶向PDK

二氯乙酸盐(dichloroacetic acid，DCA)是一种PDK1抑制剂，在临床前试验中证明其可降低HIF转录活性，抑制肿瘤内血管形成，并通过增加PDH的活性逆转肾癌细胞的有氧糖酵解，重新激活线粒体功能[122]。DCA是唯一一种进入Ⅱ期临床试验的PDK抑制剂，但较弱的抗癌作用及多种不良反应限制了其临床应用[123]。有研究表明，DCA可改善肝细胞癌对索拉菲尼的药物抵抗[124]，提示可尝试PDK抑制剂与现有靶向药物联用于肾癌的治疗。目前发现多种PDK抑制剂，如Hordenine[125]、JX06[126]及各种DCA衍生物，均在肿瘤体外模型中表现出一定的治疗作用[127]。

3.3 靶向乳酸生成和转运途径相关蛋白

ccRCC细胞内糖酵解途径的过度激活导致大量的丙酮酸在细胞内积累。为了缓解这种积累，ccRCC细胞通过上调乳酸脱氢酶和单羧酸转运蛋白的表达，加速丙酮酸转变为乳酸，并将其排出细胞外[3,4]。这一代谢调整使得肿瘤细胞能够在酸性环境中生存，并维持其快速增长和高代谢活性。由于LDH和MCT在ccRCC细胞中的重要作用，它们成为了潜在的抗肿瘤治疗靶点。抑制这些关键酶的活性可以减少乳酸的产生和排出，从而导致肿瘤细胞内乳酸积累，酸性环境加强，最终抑制

肿瘤细胞的生长和生存。

3.3.1 靶向LDH

FX11是一种LDHA抑制剂，已在肾癌小鼠移植模型中证明可增加肿瘤细胞耗氧量和活性氧的产生，并诱导细胞凋亡[128]。表没食子儿茶素-3-没食子酸酯(epigallocatechin-3-gallate，EGCG)能抑制LDHA，抑制包括肾癌在内的多种肿瘤细胞生长[129,130]，是一种具有潜力的天然提取的抗肿瘤药物。LDHA抑制剂(Galloflavin)[131-134]和草氨酸(oxamate)[135-137]均已在细胞和动物实验中证明对肿瘤细胞生长具有抑制作用，并且已在人源化小鼠模型中证明，草氨酸能增强帕博利珠单抗治疗非小细胞肺癌的疗效[138]。天然化合物水飞蓟素(silibinin)也表现出LDH的抑制活性[139]，通过调节Wnt/β-catenin信号通路，在体外和体内有效抑制RCC转移和上皮-间充质转化(EMT)[140]。喹啉-3-磺酰胺基化合物(quinoline 3-sulfonamides-based compounds)是一类高选择性且强效的LDHA抑制剂，可显著抑制肿瘤细胞内乳酸的生成，但其药代动力学特性限制了其在体内的应用[141]。槲皮素(quercetin)是一种具有生物活性的类黄酮，对PFKB和LDH均有抑制作用，可通过同时抑制HK2、PFKP和LDH抑制癌细胞的糖酵解而抑制其增殖[142]。尽管LDHA抑制剂在细胞和动物实验中表现出一定抗肿瘤效果，目前尚无LDH抑制剂用于肿瘤治疗的临床试验报道，LDH抑制剂对ccRCC治疗的临床价值值得进一步研究。

3.3.2 靶向MCTs

一项肾癌细胞和血管上皮联合培养的体外实验证明，MCTs抑制剂7ACC1能够减少RCC细胞乳酸的外排，减弱肿瘤细胞的酸性环境，抑制RCC细胞的侵袭和迁移能力，并能抑制血管内皮生成[56]。这种抑制作用可能是由于乳酸外排受限导致肿瘤细胞酸中毒及乳酸的积累影响上游的代谢而减缓糖酵解[56]。二甲双胍可促进细胞对葡萄糖的利用，加快乳酸的产生，其与MCT抑制剂联用时可产生协同作用[143,144]，进一步加强对肿瘤细胞的抑制作用。昔洛舍平(syrosingopine)对MCT1和MCT4有双重抑制作用，在与二甲双胍联用时可杀死白血病患者血液样本里的癌细胞而不损害样本内的正常血液细胞[143]。MCT1抑制剂AZD3965在晚期实体肿瘤患者中进行了Ⅰ期临床试验(NCT01791595)，证明了其在治疗剂量下的安全性[145]。但AZD3965对MCT4的抑制作用不明显，而RCC中MCT1和MCT4表达都升高，可能造成对AZD3965单药治疗的耐药[146]。有研究发现，AZD3965还可抑制脂质物质生成，并增加肿瘤微环境中树突状细胞(DC)及NK细胞的浸润[147]。目前已有多种MCTs抑制剂被发现，如VB127[148]、CYT-851[149]、AR-C15558[150]等，但仍需在肾癌模型中进行更进一步的探索。

4 总结与展望

ccRCC以代谢重编程为显著特征，导致代谢过程发生改变。由于VHL的失活导致HIF在ccRCC中堆积，增加了葡萄糖向细胞内的转运。糖酵解途径被上调以快速提供ATP为肿瘤的生长获得早期优势，并且在糖酵解过程中产生的乳酸通过上调的MCT转运至细胞外为肿瘤生长提供酸性环境以抑制免疫细胞，细胞内的乳酸还能为合成脂肪、胆固醇等产物提供原料。ccRCC细胞的糖代谢与正常细胞的差异性为靶向“糖代谢重编程”的治疗提供了可能。随着对ccRCC“糖代谢重编程”认识的进一步深入，针对“糖代谢重编程”的治疗或许会成为另一种治疗ccRCC的重要方法。

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