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·胃肠肝胆专栏·

有氧糖酵解在肝癌中的研究进展

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[摘 要] 肝癌的发病率及病死率居全球恶性肿瘤的第5位和第3位,其中肝细胞癌(HCC)占原发性肝癌的90%。有氧糖酵解首次在HCC中被发现,作为肝癌细胞能量代谢的标志,可调节细胞增殖、免疫逃逸、侵袭、转移及耐药等。糖酵解主要有3个限速酶,即磷酸果糖激酶1(PFK-1)、丙酮酸激酶M2(PKM2)和己糖激酶2(HK2),这些限速酶在糖酵解过程中发挥着重要作用,并受到多种机制调控。有氧糖酵解在HCC发生发展中具有重要作用,靶向阻断其通路中的关键因子,可成为肝癌的潜在治疗措施。随着有氧糖酵解关键酶激动/抑制剂的发展,其靶向治疗的前景值得期待。因此,本文对肝癌有氧糖酵解的研究进展作一综述,总结有氧糖酵解在肝癌发展及治疗中的作用,以期为临床提供参考。

[关键词] 有氧糖酵解;关键酶;肝细胞癌;己糖激酶;Warburg效应;丙酮酸激酶
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Research progress of aerobic glycolysis in liver cancer

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Abstract: Liver cancer has the fifth morbidity and the third mortality among maligant tumors in the worldwide, and hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancer. Aerobic glycolysis, as a hallmark of hepatoma cell energy metabolism, is firstly found in HCC and responsible for the regulation of cell proliferation, immune evasion, invasion, metastasis, and drug resistance. There are three rate-limiting enzymes in the glycolysis, including phosphofructokinase 1 (PFK1), pyruvate kinases type M2 (PKM2) and hexokinase 2 (HK2), which play an important role in the regulation of aerobic glycolysis and can be regulated by many mechanisms. Because of the importance of aerobic glycolysis in the occurrence and development of HCC, targeting and blocking key factors in its pathway may be a potential therapeutic treatment for HCC. With the development of key enzymes activations/inhibitors of aerobic glycolysis, the prospect of targeted therapy should be expected. Therefore, this article reviews the research progress of aerobic glycolysis in liver cancer, and summarize the role of aerobic glycolysis in the development and treatment of liver cancer, in order to provide clinical reference.

Keywords: aerobic glycolysis; key enzymes; hepatocellular carcinoma; hexokinase; Warburg effect; pyruvate kinases

糖代谢异常是肿瘤细胞能量代谢异于其他细胞的特征,即使在有氧环境中,肿瘤细胞仍然依赖糖酵解作为其主要的糖代谢方式提供ATP——Warburg效应[1]。Warburg效应的产生可能与肿瘤处于相对缺氧的微环境中有关,肿瘤细胞可利用糖酵解代谢的中间产物为增殖、侵袭合成大量的酯类、氨基酸、核酸等大分子物质[2]。

原发性肝癌是全球常见的恶性肿瘤之一,其发病率及病死率居全球恶性肿瘤的第5位和第3位,约90%的原发性肝癌是肝细胞癌(hepatocellular carcinoma, HCC)[3-4]。有氧糖酵解是HCC能量代谢的标志,可调控HCC细胞的增殖、侵袭、免疫逃逸、转移、血管生成及耐药等过程[5-6]。糖酵解主要有3个限速酶,即己糖激酶2(hexokinase 2, HK2)、磷酸果糖激酶1(phosphofructokinase 1, PFK-1)、丙酮酸激酶M2(pyruvate kinases type M2, PKM2)。控制有氧糖酵解中的限速酶,可抑制肿瘤生长,有望成为肝癌治疗的潜在靶点[7]。本文就有氧糖酵解关键酶对肝癌细胞增殖、侵袭的作用及其潜在治疗价值作一综述。

1 己糖激酶(hexokinase, HK)

HK是有氧糖酵解过程中第一个限速酶,能催化葡萄糖转化为葡萄糖-6-磷酸。HK有4种异构体(HK1、HK2、HK3、HK4),在大多数正常组织中只表达HK1,正常肝及胰腺组织主要通过HK4进行糖酵解,不表达HK1或HK2,然而在肝癌细胞中HK2明显高表达,在肿瘤发展过程中不同结构的HK之间可发生转换,并且HK2表达与患者肿瘤分期及预后有关[8-9]。

目前已经在肝癌和胶质母细胞瘤中观察到HK2

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的稳定表达,而且HK2的表达与患者总体生存率明显相关。Guzman等[10]研究发现,HK2在HCC发生前已升高,可作为有肝硬化背景的HCC患者潜在风险评估的生物标志物。4种异构体中,HK2促进有氧糖酵解的效率最高,其与线粒体外膜上电压依赖性阴离子选择通道蛋白1相互作用并结合,提高ATP相关合成酶的活性,从而增加ATP的产生,抑制凋亡。有研究显示,通过高通量测序,筛选功能性miRNA,发现有较多miRNAs通过HK2对肝癌细胞糖代谢起调控作用[11]。

DeWaal等[8]在敲除HK2有氧糖酵解和氧化磷酸化的研究中发现,虽在敲除HK2的人肝癌细胞系中没有发现糖代谢率改变,但在小鼠肝癌模型中HK2缺失可抑制肿瘤的发生,在人肝癌细胞中沉默HK2可抑制肿瘤发生并加速肿瘤死亡。自噬与糖酵解也存在相互关联,糖酵解与肝癌自噬水平呈负相关。研究发现,HK2的自噬降解参与糖酵解的调控,高表达HK2和高表达自噬受体蛋白组合对疾病预后的评估有指导意义[12]。

Guzman等[10]研究表明,HK2与肝癌的发生发展密切相关,与HCC患者预后呈负相关,并且可能成为肝硬化患者预测肝癌发生的标志物。在HK2对肝癌作用机制的研究中发现,在细胞水平及动物水平敲除HK2可抑制肝癌的发展[8],但HK2抑制剂用于治疗HCC仍有一定不足,有待日后进一步研究。

2 PFK-1

糖酵解的代谢效率受到多个层次、不同机制的调控,其中果糖-6-磷酸通过PFK-1合成1,6-二磷酸果糖,是糖酵解重要的限速酶[13]。PFK-1家族共有4个同工酶——PFKFB1~4,尽管这几个同工酶的同源性很高(85%),但各自有着不同的功能、属性及活性,其中PFKFB3是家族中活性最强的磷酸激酶[14-15]。

PFKFB3几乎在所有需要进行糖代谢的细胞内表达,在快速生长的组织中表达量较高;在实体肿瘤与非实体肿瘤有丝分裂过程中PFKFB3的表达会明显上调,同时也高表达于缺氧、炎症刺激以及DNA合成阶段的细胞中[16]。PFKFB3也被认为可增强糖酵解并促进肿瘤细胞的增殖、侵袭和转移[17]。有研究显示,PFKFB3与肿瘤发生发展有关,可能通过RAS、mTOR等通路调控肿瘤细胞的增殖[15]。研究发现,PFK-1丢失与肝癌的不良预后明显相关,PFK-1丢失可造成肝星状细胞衰老或衰老相关的表型表达,从而促进HCC的生长[18]。在许多恶性肿瘤中,PFKFB3的高表达与淋巴结转移、不良预后有关。靶向抑制PFKFB3可能是一种潜在治疗肝癌的新方法[19]。

PFKFB3可通过调控细胞周期通路促进肿瘤细胞的增殖。Peng等[20]发现,PFKFB3不仅在肝癌细胞内发生作用,还可通过NF-κB通路在肝癌细胞浸润的单核细胞中起作用;在HCC临床样本中可观察到PFKFB3的表达水平与CXCL2/CXCL8水平呈正相关,NF-κB通路被抑制可抑制CXCL2/CXCL8的表达,但PFKFB3与NF-κB的具体调控机制目前仍不明确。PFKFB3可进入细胞核,调控细胞周期蛋白依赖性激酶的活性。在肝癌细胞中敲低PFKFB3,可损伤DNA修复功能,从而抑制肝癌细胞增殖,导致G2/M期细胞周期阻滞,进而导致细胞死亡[21]。

血管生成是肿瘤发生的重要标志,PFKFB3在肿瘤血管生长中扮演重要角色。PFKFB3可通过血管内皮生长因子(vascular endothelial growth factor,VEGF)诱导血管生成,促使内皮细胞形成丝状足和片状足,并形成有方向的迁移[22]。PFKFB3刺激血管生成还可通过激活HIF-1α和上调VEGFR2等机制实现[23]。

PFKFB3还可通过免疫调节作用调控肿瘤细胞增殖,特别是对免疫细胞的能量代谢途径进行调控,Chesney等[24]发现,PFKFB3依赖性代谢途径的靶向治疗增强了抗肿瘤免疫反应,并有助于降低对其他肿瘤免疫疗法的耐药性。Mondal等[25]研究发现,使用PFKFB3的抑制剂PFK-158,能减少肿瘤浸润的Th17细胞和骨髓源性抑制细胞,使B16-F10荷瘤裸小鼠中肿瘤CD_8^+和CD_4^+ T细胞淋巴增加。Chen等[26]对肝癌细胞中PFKFB3-PD-L1轴研究发现,诱导肿瘤相关单核细胞中PFKFB3上调,不仅是调节细胞代谢的开关,而且还通过激活这些细胞中的NF-κB通路来介导PD-L1的表达增加,从而促进肿瘤进展。然而PFKFB3在各类免疫细胞中的作用非常复杂,其通过免疫调节调控肿瘤生长的机制仍需探索。

PFK-1是糖代谢的重要调控因子,不仅广泛存在于正常组织中,在肿瘤组织中也起到了重要的调控作用。其中活性最强的PFKFB3在肝癌组织中起主要作用,可以通过调控细胞周期、血管生成、免疫微环境等方式影响肿瘤细胞的增殖。PFKFB3在HCC组织中表达量明显增高,与HCC的预后呈正相关,靶向抑制PFKFB3可能成为治疗HCC的潜在靶点。

3 丙酮酸激酶(pyruvate kinases, PK)

PK是糖酵解过程中的最终限速酶,可催化磷酸烯醇式丙酮酸(phosphoenolpyruvate,PEP)生成丙酮酸和ATP,主要包括肝型、红细胞型、肌肉同工酶型(PKM1、PKM2)等亚型,其中PKM2主要存在于肿瘤等快速生长的组织中,与肿瘤患者预后不良显著相关[27];通常认为异常的酪氨酸激酶信号传导驱动了肿瘤生长,而PKM2就是酪氨酸激酶重要的信号靶点之一[28]。

PKM2对肿瘤的调控作用是近些年来研究的热

点,PKM2主要通过经典活性和非经典活性途径在肿瘤Warburg效应中起作用[27]。PKM2的活性主要受其聚合状态所调控,一种为四聚体形式,酶活性较高,位于胞浆内,能迅速将PEP转化为丙酮酸,增加糖酵解速率,产生更多ATP;另一种形式是低酶活性的二聚体或单体,可转移至细胞核内辅助激活下游的转录因子。PKM2在肿瘤生长中的作用机制非常复杂,受到很多因素调节,其变构状态与周围环境明显相关[29]。PKM2的作用机制与其他磷酸酪氨酸结合蛋白不同,磷酸化后酶活性降低,由高活性的四聚体形式转化为低活性的二聚体形式,但其促进了乳酸生成和肿瘤生长。PKM2二聚体虽酶活性较低,但可促进中间代谢产物迅速合成肿瘤必须的氨基酸、酯类等大分子,是保证Warburg效应的必要条件[30-31]。

研究表明,PKM2二聚体可通过激活HIF-1α、β-actin/c-Myc、NF-κB等通路调控肿瘤细胞生长[32]。PKM2进入细胞核可促进靶基因转录,如HIF-1α靶向表达GLUTs、LDHA、VEGF等,还可正反馈调节糖酵解,使血管生长,从而促进肿瘤的发生[33]。PKM2除了在转录水平中起调控作用外,同时还通过翻译后修饰对蛋白定位、酶活性、稳定性等过程进行调控[34]。

PKM2活性与肿瘤细胞增殖的调控关系在大量肿瘤模型中已被证明,但PKM2缺失是否会促进肿瘤生长仍有争议[35]。Dayton等[36]研究发现,PKM2缺失的小鼠品系是可生长、繁殖、发育的,因此PKM2不是胚胎或生长发育所必需的;同时PKM2缺失致肝细胞自发癌变的概率明显增加,并随着全身葡萄糖稳态、炎症、肝脂肪变性等状态所改变。研究发现,PKM2活性与肿瘤细胞增殖有关,如使用PKM2小分子抑制剂(紫草素)处理细胞,细胞毒性随紫草素浓度增加而增加,从而导致肿瘤细胞增殖速度减慢[37];姜黄素亦可抑制肿瘤细胞增殖,其介导的PKM2表达减少,可导致葡萄糖消耗和乳酸生成减少,细胞增殖减慢[38]。有趣的是,紫草素抑制PKM2活性、姜黄素降低PKM2表达、PKM2在体内的缺失都可导致糖酵解速度减慢、乳酸浓度下降;但PKM2活性下降导致肿瘤细胞增殖减慢,而PKM2缺失却加速肿瘤形成,显示出PKM2在肿瘤中的不同作用。PKM2可能兼有促进和抑制肿瘤生长的双重作用,并且其活性在癌症中普遍下调,但PKM2在Warburg效应中显示出酶活性下降而糖酵解增加的矛盾现象[39-41]。

PKM2活性状态对肿瘤的调控作用一直存在争议,因为PKM2抑制剂可抑制肿瘤生长,而在部分肿瘤中敲除PKM2可促进肿瘤增殖,所以PKM2活性在某些肿瘤模型的研究结果中存在争议。因此,PKM2促进或抑制肿瘤生长的作用复杂,并且十分依赖环境和肿瘤生长模型,这可能是肿瘤研究中PKM2作用各不相同的原因之一。

4 小结

糖酵解的限速酶在肿瘤能量代谢中起着重要作用,尤其在肝癌中,3个关键限速酶及其同工酶贯穿了肝癌的发生和发展,可能是未来肝癌治疗领域中的一个重要靶点。本文总结了大量相关研究,强调关键限速酶通过糖酵解对肿瘤细胞增殖、迁移、凋亡和自噬等过程的调控作用。虽然近年来对于肿瘤能量代谢重编程研究有很多新发现,但仍有较多未完全阐明的机制;肿瘤能量代谢重编程的相关药物和相关分子机制的研究可能是未来肿瘤治疗的新方向。

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