魏民博士，东北师范大学生命科学学院教授，博士生导师，细胞生物学重点学科方向带头人，分子表观遗传学教育部重点实验室副主任。兼任国务院学位委员会学科评议组成员、中国细胞生物学学会理事、吉林省细胞生物学学会理事长等。主要从事细胞代谢调控机制的研究，重点关注代谢关键酶的蛋白质翻译后修饰调控肿瘤细胞增殖及免疫细胞激活与分化的分子机制，致力于为细胞代谢与细胞重要生命活动的协调统一性提供新理解。主持国家自然科学基金项目5项，已在*Nat Immunol*、*Proc Natl Acad Sci USA*、*eLife*、*Cell Rep*、*J Biol Chem*、*J Immunol*等期刊上发表SCI论文30余篇。

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糖脂代谢关键酶在肿瘤细胞增殖中的作用研究进展

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摘要 近年来，代谢酶作为肿瘤细胞代谢调控的直接执行者备受关注。研究发现，一些关键代谢酶可以通过多种方式改变自身活性以及获得非代谢酶功能，从而驱动肿瘤细胞的代谢重编程。这些方式主要包括异常表达、突变、蛋白质翻译后修饰改变、寡聚状态变化以及亚细胞定位的易位等。该文主要关注肿瘤细胞糖脂代谢途径中的关键调节酶，对其活性和功能改变及其在肿瘤细胞的生物大分子合成、能量供给及氧化还原平衡等三个方面的作用研究进展进行综述，以期为肿瘤的研究和治疗提供新思路。

关键词 肿瘤细胞增殖; 肿瘤细胞代谢; 糖脂代谢; 代谢酶

Key Enzymes in Glucose and Lipid Metabolism and Their Functions in Tumor Cell Proliferation

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Abstract In recent decades, metabolic enzymes have attracted a tremendous amount of attention due to their central role in the control of tumor cell metabolism. Specific enzymes can change their enzymatic activity through multiple manners, including abnormal expression, gene mutation, post-translational modification, and altered oligomerization and sub-cellular localization. Sometimes, they can also function as non-metabolic enzymes to regulate different cellular events. This review focuses on enzymes involved in glucose and lipid metabolism in rapidly proliferating tumor cells, and emphasizes biological consequences from alterations in their activity and func-

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tion. By discussing the three basic needs of tumor cells: increased biosynthesis of macromolecules, high demand of energy and balanced cellular redox status, this review will provide insights into tumor-associated research and therapeutic treatments against cancers.

Keywords tumor cell proliferation; tumor cell metabolism; glucose and lipid metabolism; metabolic enzyme

美国科学家WEINBERG等[1]在2011年总结了肿瘤的十大特征, 首次将“异常代谢”新增为肿瘤的特征之一。实际上, 早在1924年, 德国科学家WARBURG就提出了肿瘤细胞“有氧糖酵解”(aerobic glycolysis)的概念, 即与已分化的细胞相比, 增殖的肿瘤细胞即使在氧气充足的条件下, 也会消耗大量的葡萄糖进行糖酵解代谢而非有氧氧化, 并产生大量的乳酸, 后人也称其为“Warburg效应”[2]。虽然距首次发现肿瘤细胞代谢特征已过去近一个世纪, 但直到最近十几年, 肿瘤异常代谢的研究才又重新引起了人们的广泛关注, 并迅速成为肿瘤学研究的热点。

肿瘤细胞的持续分裂为其代谢“提出”了三大挑战: 其一, 需要细胞重要组分的加倍, 即增强生物大分子合成, 这也是细胞分裂的基本前提; 其二, 需要充足的能量供给; 其三, 需要充足的还原力以维持细胞内氧化还原平衡[3]。显然, 肿瘤细胞必须要改变其代谢策略, 才能“应对”这些挑战。例如, “有氧糖酵解”就是肿瘤细胞“选择”的一项策略, 其益处主要在于糖酵解途径有两个非常重要的代谢支路: 磷酸戊糖途径(pentose phosphate pathway, PPP)和丝氨酸合成途径(serine synthesis pathway, SSP)。PPP的主要代谢产物为5-磷酸核糖和NADPH, 其中5-磷酸核糖是核苷酸生物合成的前体分子, 而NADPH既可以为生物大分子的合成提供还原力, 也可用于平衡细胞持续增殖时产生的氧化压力。SSP的主要代谢产物是丝氨酸和甘氨酸, 它们既可用于蛋白质的生物合成, 也可在丝氨酸向甘氨酸转化的过程中产生一碳单位, 而一碳单位经叶酸循环代谢为核苷酸的生物合成提供前体物质, 并在此过程中产生NADPH[4]。由此可见, 肿瘤细胞采用“有氧糖酵解”的一个重要原因就是为了增强糖酵解的支路代谢, 用以满足其对生物大分子合成和氧化还原平衡的需要。又如, 相对于大多已分化细胞主要进行脂肪酸氧化代谢, 增殖的肿瘤细胞则是“选择”脂肪酸的从头合成, 其主要原因就是为了实现膜脂的加倍, 满足细胞分裂的物质需要[5]。

本文将围绕肿瘤细胞持续增殖的基本代谢需求, 即生物大分子合成、能量供给及氧化还原平衡等三个方面, 系统总结糖脂代谢关键酶在肿瘤细胞增殖过程中发生的活性和功能改变。

1 肿瘤细胞的生物大分子合成

细胞分裂的基本前提是细胞重要组分的加倍。因此, 持续分裂的肿瘤细胞需要进行旺盛的生物合成代谢来满足其对核酸、蛋白质、脂质等生物大分子的需求[3]。简言之, 肿瘤细胞从外界摄取葡萄糖等营养物质, 通过对糖脂代谢等多条代谢途径进行重新编程, 为生物大分子的合成提供保证。在此过程中, 多种关键代谢酶发挥了重要调控作用。

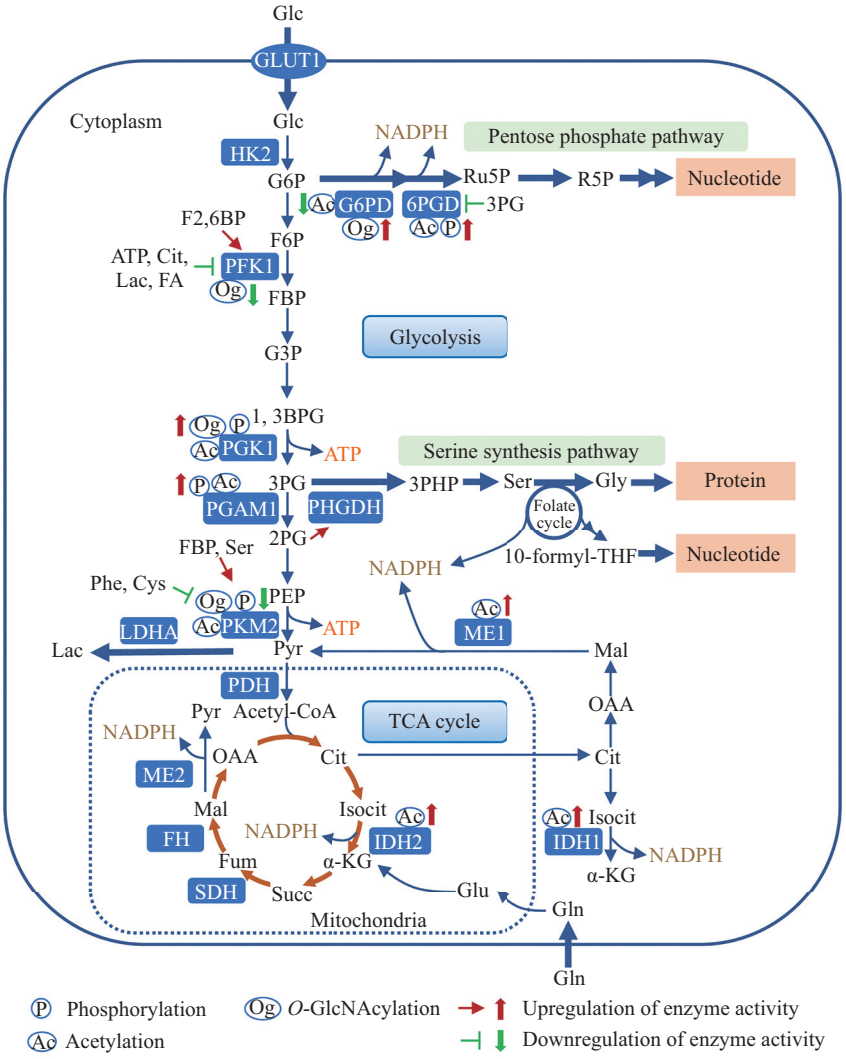
1.1 己糖激酶(hexokinase, HK)

HK是糖酵解途径的第一个限速酶, 催化葡萄糖生成6-磷酸葡萄糖(图1), 该反应既为后续代谢提供了底物, 又保证了葡萄糖进入胞内后不会被运出胞外。HK有四种亚型, 其中HK1主要分布在脑中; HK2主要分布在心肌、脂肪组织和骨骼中; HK3主要分布在肝、肾和肠组织中; HK4又名葡萄糖激酶, 主要分布在肝脏中, 参与糖原合成。在这四种亚型中, HK1和HK2具有相对较高的催化效率, 它们均具有一段N-端疏水氨基酸序列, 可与线粒体外膜电压依赖性阴离子通道(voltage-dependent anion channel, VDAC)结合, 这使得线粒体产生的ATP可以快速被HK1和HK2所利用, 且HK1和HK2可迅速将进入胞内的葡萄糖磷酸化[6]。

有氧糖酵解是肿瘤细胞进行生物合成的主要代谢途径, 而HK作为该途径的第一个限速酶, 其高活性对于有氧糖酵解代谢的底物供给非常重要。目前发现, HK2在多种肿瘤细胞中是显著高表达的[7]。而且, 与线粒体VADC结合的HK2水平明显增加, 这使得HK2催化的酶促反应速度加快, 促进糖酵解代谢[8]。对肝癌和卵巢癌患者的随访也显示, HK2的高表达与肿瘤复发和耐药性相关, 且HK2高表达患者的生存期更短[9-10]。

1.2 磷酸果糖激酶1(phosphofructokinase 1, PFK1)

PFK1是糖酵解途径的第二个限速酶, 催化6-磷



1,3BPG: 1,3-二磷酸甘油酸; 2PG: 2-磷酸甘油酸; 3PG: 3-磷酸甘油酸; 3PHP: 3-磷酸羟基丙酮酸; 6PGD: 6-磷酸葡萄糖酸脱氢酶; 10-formyl-THF: 10-甲基四氢叶酸; α-KG: α-酮戊二酸; Acetyl-CoA: 乙酰CoA; Cit: 柠檬酸; Cys: 半胱氨酸; F2,6BP: 2,6-二磷酸果糖; F6P: 6-磷酸果糖; FBP: 1,6-二磷酸果糖; FH: 延胡索酸酶; Fum: 延胡索酸; G3P: 三磷酸甘油醛; G6P: 6-磷酸葡萄糖; G6PD: 6-磷酸葡萄糖脱氢酶; Glc: 葡萄糖; Gln: 谷氨酰胺; Glu: 谷氨酸; GLUT1: 葡萄糖转运蛋白1; Gly: 甘氨酸; HK2: 己糖激酶2; IDH: 异柠檬酸脱氢酶; Isocit: 异柠檬酸; Lac: 乳酸; LDHA: 乳酸脱氢酶A; Mal: 苹果酸; ME: 苹果酸酶; OAA: 草酰乙酸; PDH: 丙酮酸脱氢酶; PEP: 磷酸烯醇式丙酮酸; PFK1: 磷酸果糖激酶1; PGAM1: 磷酸甘油酸变位酶1; PGK1: 磷酸甘油酸激酶1; Phe: 苯丙氨酸; PHGDH: 3-磷酸甘油酸脱氢酶; PKM2: 丙酮酸激酶2; Pyr: 丙酮酸; R5P: 5-磷酸核糖; Ru5P: 5-磷酸核酮糖; SDH: 琥珀酸脱氢酶; Ser: 丝氨酸; Succ: 琥珀酸。

1,3BPG: 1,3-bisphosphoglycerate; 2PG: 2-phophoglycerate; 3PG: 3-phosphoglycerate; 3PHP: 3-phosphate hydroxypyruvate; 6PGD: 6-phosphogluconate dehydrogenase; 10-formyl-THF: 10-formyl-tetrahydrofolate; α-KG: α-ketoglutarate; Acetyl-CoA: acetyl coenzyme A; Cit: citrate; Cys: cysteine; F2,6BP: fructose-2,6-bisphosphate; F6P: fructose-6-phosphate; FBP: fructose-1,6-bisphosphate; FH: fumarate hydratase; Fum: fumarate; G3P: glyceraldaldehyde-3-phosphate; G6P: glucose-6-phosphate; G6PD: glucose-6-phosphate dehydrogenase; Glc: glucose; Gln: glutamine; Glu: glutamate; GLUT1: glucose transporter 1; Gly: glycine; HK2: hexokinase 2; IDH: isocitrate dehydrogenase; Isocit: isocitrate; Lac: lactate; LDHA: lactate dehydrogenase A; Mal: malate; ME: malic enzyme; OAA: oxalacetic acid; PDH: pyruvate dehydrogenase; PEP: phosphoenolpyruvate; PFK1: phosphofructokinase 1; PGAM1: phosphoglycerate mutase 1: PGK1: phosphoglycerate kinase 1; Phe: phenylalanine; PHGDH: 3-phosphoglycerate dehydrogenase; PKM2: pyruvate kinase 2; Pyr: pyruvate; R5P: ribose-5-phosphate; Ru5P: ribulose-5-phosphate; SDH: succinate dehydrogenase; Ser: serine; Succ: succinate.

图1　肿瘤细胞糖代谢的关键酶

Fig. 1　The key enzymes in tumor glucose metabolism

酸果糖生成1,6-二磷酸果糖(图1), 其活性形式为同源或异源四聚体。乳酸可通过促进PFK1四聚体的解聚, 降低其活性[11]。此外, ATP、柠檬酸及长链脂肪酸可作为别构抑制剂降低PFK1活性[12-13]。PFK1的强别构激活剂是2,6-二磷酸果糖, 即使在ATP存在的情况下, 它也能提高PFK1活性[14]。

与HK的作用相同, PFK1的高活性可以保证肿瘤细胞有氧糖酵解的顺利进行。但由于PFK1催化的

反应上游存在PPP代谢支路(图1), 因此该酶的活性在肿瘤细胞生物大分子合成过程中受到严格调控。研究发现, 在多种肿瘤细胞中, PFK1活性明显升高, 且与细胞增殖能力显著相关[13]。一项肝癌及宫颈癌的研究发现, PFK1活性上升是由它的强别构激活剂2,6-二磷酸果糖的水平升高所导致的[15]。另有研究发现, 在低氧条件下, 肺癌细胞中PFK1的Ser529位点发生*O*-GlcNAc糖基化修饰, 导致其活性降低, 使上游产物更多地流入PPP代谢支路, 促进了肿瘤细胞增殖[16]。以上研究表明, 肿瘤细胞的代谢改变具有灵活性, 不同组织来源的肿瘤细胞会根据其所处的微环境差异, “采用”有利于其存活和增殖的最优策略。

1.3 丙酮酸激酶(pyruvate kinase, PK)

PK是糖酵解途径的最后一个限速酶, 催化磷酸烯醇式丙酮酸生成丙酮酸和ATP(图1)。PK有四种亚型, 其中PKL和PKR分别表达于肝脏和红细胞; PKM1主要表达于骨骼肌和大脑; PKM2主要表达于快速增殖的细胞, 包括肿瘤细胞[17]。PKL、PKR和PKM1均是以结构稳定的活性四聚体形式存在, 而PKM2则是以活性四聚体、低活性二聚体和无活性单体三种形式存在, 其寡聚状态受1,6-二磷酸果糖、丝氨酸、苯丙氨酸和半胱氨酸等多种别构效应因子调节[18]。

如前所述, PKM2是肿瘤细胞PK的主要亚型, 因PPP和SSP代谢支路均位于其催化反应的上游, 故其低活性将有助于上游产物流入生物大分子合成支路(图1)。PKM2的寡聚状态是影响其活性的主要因素, 现已发现多种蛋白质翻译后修饰可以调控肿瘤细胞PKM2的寡聚状态。例如, PKM2 Ser37的磷酸化[19]、Tyr105的磷酸化[20]、Lys433的乙酰化[21]、Thr405/Ser406的*O*-GlcNAc糖基化[22]等, 均可分别促进PKM2四聚体解聚, 降低其活性, 促进肿瘤细胞的合成代谢。此外, 还有研究发现, 解聚后的PKM2发生了核易位, 并可作为转录调节因子增强HIF1α、Myc等转录因子的活性, 进而上调葡萄糖转运子1和乳酸脱氢酶A的基因表达, 进一步增强肿瘤细胞的有氧糖酵解代谢[23]。

1.4 磷酸甘油酸变位酶(phosphoglycerate mutase, PGAM)

PGAM是糖酵解途径中的非限速酶, 催化3-磷酸甘油酸生成2-磷酸甘油酸(图1), 它有两种亚型, 其中PGAM1表达于大多数组织, His11位点发生磷酸化是其主要的活化形式[24-25]; PGAM2高表达于肌肉组织。该酶的特殊之处在于, 其底物3-磷酸甘油酸是PPP代谢支路中唯一限速酶的竞争性抑制剂, 其产物2-磷酸甘油酸是SSP代谢支路中第一个限速酶的别构激活剂[26]。因此, 提高PGAM的活性可以同时增强糖酵解途径中的两个最重要的合成代谢支路。显而易见, 这对于促进肿瘤细胞的生物大分子合成非常重要。

研究表明, 在肺癌、直肠癌、肝癌和乳腺癌等组织中, PGAM1的表达量和活性均显著提高[27-28]。目前已发现抑癌基因*p53*的缺失可显著上调PGAM1的表达[29-31]。另外, 肿瘤细胞PGAM1 Tyr26位点可在致癌酪氨酸激酶(oncogenic tyrosine kinase, OTK)的作用下发生磷酸化, 使处于活化状态的PGAM1(His11磷酸化)更加稳定[32]。此外, 肿瘤细胞PGAM1 Lys100发生的乙酰化修饰可显著增强其活性, 促进细胞增殖[33]。

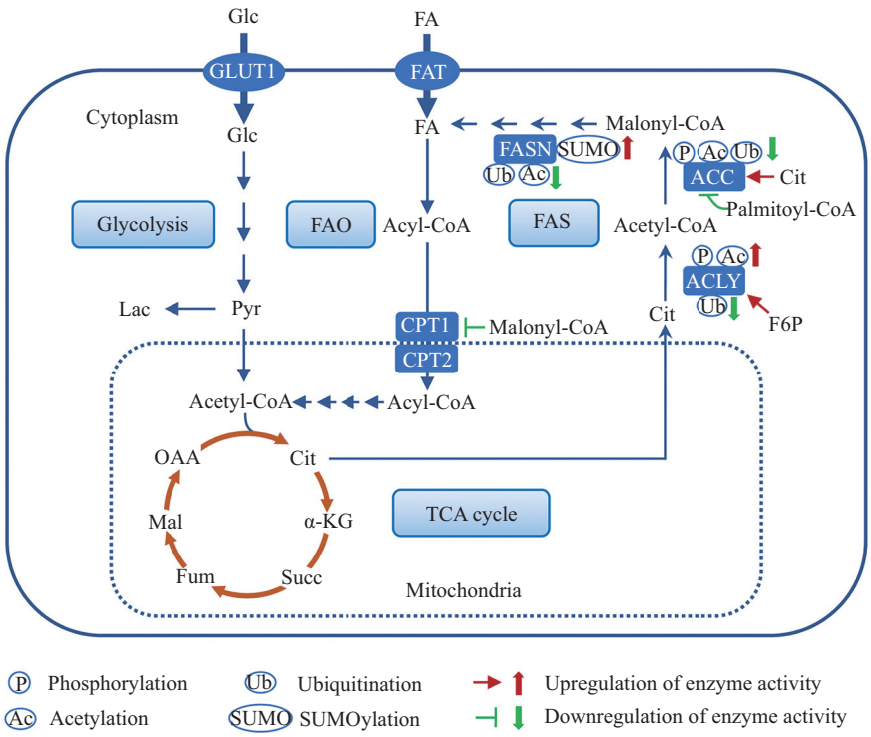
1.5 ATP-柠檬酸裂解酶(ATP-citrate lyase, ACLY)

ACLY是脂肪酸从头合成途径的第一个限速酶, 在ATP存在的条件下, 催化柠檬酸裂解为乙酰CoA和草酰乙酸, 为脂肪酸的从头合成提供原料(图2)。ACLY Ser455发生磷酸化是其主要活化形式, 该磷酸化修饰由AKT直接催化[34]。此外, ACLY可受糖酵解中间产物6-磷酸果糖的别构激活[5]。

脂肪酸从头合成增强是肿瘤细胞的另外一个典型代谢特征。作为该途径的第一个限速酶, ACLY的高活性对于保证脂肪酸合成原料乙酰CoA的供给非常重要。研究表明, ACLY在多种肿瘤细胞中高表达, 而且在胃癌患者的组织样本中, ACLY的高表达与晚期恶性肿瘤和肿瘤细胞淋巴结转移具有相关性[35]。使用化学抑制剂或遗传学手段下调ACLY活性, 可显著抑制乳腺癌、结肠癌、胃癌和肺癌等多种肿瘤的细胞增殖[36-38]。此外, 在非小细胞肺癌细胞中, 乙酰基转移酶PCAF催化ACLY Lys540/546/554位点发生了高水平的乙酰化, 占据了原有的泛素化修饰位点, 从而通过防止ACLY降解, 提高了其活性[39]。

1.6 乙酰CoA羧化酶(acetyl CoA carboxylase, ACC)

ACC是脂肪酸从头合成途径的第二个限速酶, 催化乙酰CoA生成丙二酰CoA(图2)。ACC有两个亚型, 其中ACC1定位于胞质中, 主要表达于肝脏和脂肪组织; ACC2定位于线粒体外膜, 主要表达于心肌



α-KG: α-酮戊二酸; ACC: 乙酰CoA羧化酶; Acetyl-CoA: 乙酰CoA; ACLY: ATP-柠檬酸裂解酶; Acyl-CoA: 脂酰CoA; Cit: 柠檬酸; CPT1: 肉碱棕榈酰转移酶1; F6P: 6-磷酸果糖; FA: 脂肪酸; FAO: 脂肪酸氧化; FAS: 脂肪酸合成; FASN: 脂肪酸合酶; FAT: 脂肪酸转位酶; Fum: 延胡索酸; Glc: 葡萄糖; GLUT1: 葡萄糖转运蛋白1; Lac: 乳酸; Mal: 苹果酸; Malonyl-CoA: 丙二酰CoA; OAA: 草酰乙酸; Palmitoyl-CoA: 棕榈酰CoA; Pyr: 丙酮酸; Succ: 琥珀酸。

α-KG: α-ketoglutarate; ACC: acetyl coenzyme A carboxylase; Acetyl-CoA: acetyl coenzyme A; ACLY: ATP-citrate lyase; Acyl-CoA: acyl coenzyme A; Cit: citrate; CPT1: carnitine palmitoyltransferase 1; F6P: fructose-6-phosphate; FA: fatty acid; FAO: fatty acid oxidation; FAS: fatty acid synthesis; FASN: fatty acid synthase; FAT: fatty acid translocase; Fum: fumarate; Glc: glucose; GLUT1: glucose transporter 1; Lac: lactate; Mal: malate; Malonyl-CoA: malonyl coenzyme A; OAA: oxalacetic acid; Palmitoyl-CoA: palmitoyl coenzyme A; Pyr: pyruvate; Succ: succinate.

图2　肿瘤细胞脂代谢的关键酶

Fig. 2　The key enzymes in tumor lipid metabolism

和骨骼肌。ACC可受柠檬酸别构激活及棕榈酰CoA别构抑制[40]。此外, ACC活性还可受蛋白质翻译后修饰调节。例如, 在空腹条件下, 小鼠脂肪组织ACC可同时发生磷酸化和泛素化修饰, 其中磷酸化导致其解聚失活, 泛素化导致其降解[41]。

与ACLY相同, ACC的高活性对促进肿瘤细胞的脂肪酸从头合成同样至关重要。研究发现, ACC1在多种肿瘤(包括乳腺癌、前列腺癌、肝癌和胃癌等)细胞中高表达[42]。临床数据显示, ACC1在肝癌组织中表达上调, 且与患者较短的总生存期和较差的疾病复发情况显著相关[43]。此外, ACC1的缺失可通过抑制脂肪酸合成, 诱导前列腺癌和乳腺癌肿瘤细胞发生凋亡, 但对非肿瘤细胞无此作用[44], 表明了ACC1在肿瘤细胞中具有独特的作用。在宫颈癌组织中, 去乙酰化酶SIRT3的高表达促进了ACC1的去乙酰化, 提高了ACC1蛋白稳定性, 进而促进脂类合成和细胞增殖[45]。另有研究发现, ACC2在喉癌中高表达, 且ACC2的表达水平与临床癌症分期和5年生存率下降呈正相关[46]。

1.7　脂肪酸合酶(fatty acid synthase, FASN)

FASN是脂肪酸从头合成途径的第三个限速酶, 催化丙二酰CoA和乙酰CoA通过连续的缩合反应生成长链脂肪酸(图2), 其活性形式为同源二聚体。

目前发现, FASN在不同类型肿瘤细胞中的表达水平普遍较高, 并被视为肿瘤预后不良的分子标志[47-48]。使用FASN的化学抑制剂可优先杀死肿瘤细胞, 其主要原因是, 与更倾向于从外界摄取脂肪酸的已分化细胞相比, 大多数肿瘤细胞更依赖于FASN介导的脂肪酸从头合成[49]。另有研究表明, 肝癌组织中的FASN乙酰化丰度较低。因为FASN的乙酰化修饰可以促进其泛素化降解, 所以FASN的低乙酰化水平会抑制其泛素化修饰的发生, 从而防止自身被降解, 有利于脂肪酸从头合成[50]。此外, FASN的蛋白稳定性也受到类泛素化修饰的调

控, 例如在乳腺癌细胞中, 类泛素化修饰可以帮助FASN抵御蛋白酶体对其的降解[51]。

2 肿瘤细胞的能量供给

细胞的持续分裂需要充足的能量供给, 而肿瘤细胞在应对生物大分子合成挑战中所采用的有氧糖酵解和脂肪酸从头合成显然不是有效的能量供给方式。WARBURG曾提出肿瘤细胞线粒体呼吸功能受损被迫采用有氧糖酵解的假说[2], 但其后的实验证据表明, 绝大多数肿瘤细胞的线粒体功能完好无损[4], 这说明有氧糖酵解是肿瘤细胞“主动选择”的结果。目前研究表明, 不同类型的肿瘤细胞因条件而异采用了不同的产能方式, 但主要包括① 谷氨酰胺回补途径: 通过促进外源摄取的谷氨酰胺向α-酮戊二酸转化, 补充因丙酮酸进入线粒体减少所致的三羧酸循环中间产物来源的不足, 三羧酸循环的部分运转即可产生大量能量, 此种产能方式被大多数肿瘤细胞所采用[52]; ② 有氧糖酵解: 虽然该途径的ATP产率低, 但通量大且快速, 因此也是能量的一个主要来源[15]; ③ 脂肪酸氧化: 某些肿瘤细胞通过增强对外源脂肪酸的摄取来驱动脂肪酸氧化代谢产能[5,53]。

2.1 磷酸甘油酸激酶(phosphoglycerate kinase, PGK)

PGK是糖酵解途径中直接催化ATP生成的酶, 催化1,3-二磷酸甘油酸生成3-磷酸甘油酸, 同时产生1分子ATP(图1)。PGK有两种亚型, 其中PGK1表达于所有体细胞; 而PGK2只表达于精子形成过程中。

对于某些类型的肿瘤细胞来说, 有氧糖酵解是其获取能量的主要方式。例如, 在肝癌和结肠癌细胞中, 有氧糖酵解对ATP生成的贡献率可达60%[54]。肿瘤细胞有氧糖酵解代谢的产能主要是依赖于PGK1, 因为糖酵解途径中的另一个催化ATP生成的酶PKM2, 在肿瘤细胞中的活性通常都是较低的(见1.3)。目前发现, PGK1在多种类型的肿瘤细胞中表达上调并促进有氧糖酵解[55]。临床数据还显示, 在多种肿瘤(包括乳腺癌、结肠癌、胶质瘤、肺癌和肝癌)组织中, PGK1的高表达与肿瘤的增殖和转移都显著相关[56]。在肿瘤细胞中, PGK1的活性还受多种蛋白质翻译后修饰调节。其Ser203的磷酸化正向调控有氧糖酵解, 促进胶质母细胞瘤发生[57]; Lys323的乙酰化提高PGK1活性, 促进肝癌发展[58]。在结肠癌细胞中, Thr255的*O*-GlcNAc糖基化修饰增强了PGK1的活性, 并介导了PGK1从胞质易位至线粒体。易位至线粒体的PGK1可作为蛋白激酶对丙酮酸脱氢酶进行磷酸化修饰, 导致其酶活性降低, 进而减少丙酮酸进入线粒体进行有氧氧化[59]。

2.2 琥珀酸脱氢酶(succinate dehydrogenase, SDH)和延胡索酸酶(fumarate hydratase, FH)

SDH和FH是三羧酸循环中紧邻的两个非限速酶, SDH催化琥珀酸生成延胡索酸; FH催化延胡索酸转化为苹果酸。

目前研究表明, 在以有氧糖酵解代谢为主要供能方式的肿瘤细胞中, 除胞质中的PGK1活性升高外, 线粒体内的代谢酶因突变导致的活性下降也是驱使肿瘤细胞更多利用有氧糖酵解供能的原因之一[60]。其中, SDH和FH是最常见的两个携带突变的代谢酶。在某些肿瘤细胞中, 携带高频突变的SDH酶活性丧失, 引起琥珀酸在线粒体内大量积累, 最终抑制线粒体呼吸功能[61]; *FH*突变导致延胡索酸在线粒体内的含量提高100倍以上, 并引发上游代谢物琥珀酸的积累达7倍以上, 同时其下游产物苹果酸和柠檬酸水平显著下降[62]。还有研究发现, *FH*突变会导致遗传性平滑肌瘤病与肾细胞癌发生, 且携带*FH*突变的肾癌会呈现出显著增强的侵袭性和不良的临床预后特征[63]。

2.3 肉碱棕榈酰转移酶(carnitine palmitoyltransferase, CPT)

CPT是脂肪酸氧化途径最重要的限速酶, 其功能是协助活化的长链脂肪酸(脂酰CoA)进入线粒体内。CPT有CPT1和CPT2两种亚型, 它们分别定位于线粒体外膜和内膜上。CPT1催化脂酰CoA与肉碱形成脂酰肉碱, 进入线粒体基质内的脂酰肉碱再经CPT2催化重新生成脂酰CoA, 进入氧化代谢途径(图2)。在两个亚型中, CPT1是更重要的限速酶, 其活性受脂肪酸从头合成途径中间产物丙二酰CoA的别构抑制。

对于某些类型的肿瘤(如前列腺癌、胃癌和非小细胞肺癌等)细胞来说, 脂肪酸氧化被认为是其主要的供能方式[53,64-65]。而且, 这些被用于氧化的脂肪酸大部分是通过脂肪酸转位酶从胞外摄取的[5]。对于这些类型的肿瘤细胞来说, CPT1的高活性是非常重要的。研究发现, CPT1在多种肿瘤细胞中异常高表达[65]。此外, 在乳腺癌细胞中, 催乳素能促进*CPT1*基因转录, 进而加速脂肪酸氧化, 促进细胞增殖; 但在正常乳腺上皮细胞中, 催乳素却无此作用[66]。在

前列腺癌和膀胱癌细胞中, 使用CPT1的特异性抑制剂Etomoxir可显著抑制其增殖能力[67-68]。在另一项乳腺癌细胞的研究中发现, 通过抑制ACC的活性, 降低其产物丙二酰CoA的水平, 可显著解除丙二酰CoA对CPT1活性的抑制, 进而促进细胞增殖[69]。

3 肿瘤细胞的氧化还原平衡

肿瘤细胞的快速增殖会伴随胞内氧化压力的升高。为此, 肿瘤细胞需要提高还原力以维持胞内氧化还原平衡。NADPH是细胞内最重要的还原力, 其功能之一是用于生物大分子的合成, 它的第二个功能就是平衡胞内的氧化压力。NADPH的生成受到细胞内多种代谢途径和酶(主要包括PPP代谢支路、叶酸循环、谷氨酰胺代谢、苹果酸酶和异柠檬酸脱氢酶等)的调控[70]。

3.1 6-磷酸葡萄糖脱氢酶(glucose-6-phosphate dehydrogenase, G6PD)和6-磷酸葡萄糖酸脱氢酶(6-phosphogluconate dehydrogenase, 6PGD)

G6PD和6PGD是PPP代谢支路中催化NADPH生成的两个酶。G6PD是该途径的第一个酶, 催化6-磷酸葡萄糖生成6-磷酸葡萄糖酸内酯和NADPH(图1)。G6PD的活性受其底物$NADP^+$的正向调节和产物NADPH的负向调节, 因此在那些低消耗NADPH的细胞中, 即使其表达量较高, 却仍然保持较低活性。6PGD是PPP代谢支路的第三个酶, 也是该途径中唯一的限速酶, 催化6-磷酸葡萄糖酸的氧化脱羧, 生成5-磷酸核酮糖和NADPH(图1)。6PGD的活性受糖酵解代谢中间产物3-磷酸甘油酸的竞争性抑制[26]。

研究发现, G6PD在多种类型肿瘤(包括膀胱癌、乳腺癌、前列腺癌和胃癌等)细胞中活性显著提高, 且其高表达也与肿瘤患者的预后不良显著相关[71-72]。在某些肿瘤细胞中还发现, Ser84的*O*-GlcNAc糖基化和Lys403的去乙酰化修饰均能增强G6PD活性, 进而提高NADPH生成量[73-74]。此外, 多种肿瘤细胞中的6PGD也异常活跃, 且与肿瘤发生发展显著相关[75]。有研究表明, 肿瘤细胞6PGD可发生Tyr481位点的磷酸化、Lys76和Lys294位点的乙酰化等, 这些修饰均可增强其酶活性[76-77]。还有一项研究发现, 当干涉肺癌细胞6PGD的表达后, 细胞内的NADPH水平并未发生变化, 可能的原因是6PGD缺失导致了$NADP^+$/NADPH值的短暂性增加, 从而增强了G6PD的活性, 补偿了因6PGD的缺失导致的NADPH生成量减少。这也提示, 在基于PPP代谢支路的相关治疗策略中, 干预G6PD可能比干预6PGD更有效。

3.2 苹果酸酶(malic enzyme, ME)

ME有三种亚型, ME1定位于细胞质; ME2和ME3定位于线粒体。在哺乳动物细胞中, ME1和ME2是ME的主要亚型。ME1催化苹果酸氧化脱羧生成丙酮酸和NADPH; 而ME2催化苹果酸生成丙酮酸和NADH或NADPH(图1)。一项肿瘤细胞的定量分析研究表明, ME对NADPH生成的直接贡献与PPP代谢支路的贡献相当[78]。

研究发现, ME1的高表达与癌症(包括胃癌、口腔鳞癌、乳腺癌、肺癌等)患者的预后不良显著相关。干涉ME1表达会显著降低细胞NADPH水平, 诱发肿瘤细胞凋亡[70]。此外, 在肿瘤细胞中也发现, ME1 Lys337位点的乙酰化修饰可增强其酶活性, 促进肿瘤细胞增殖[79]。与ME1类似, ME2在多种癌症肿瘤细胞中也高表达, 并与癌症的发生、转移和预后不良密切相关。干涉ME2表达会导致肿瘤细胞内氧化压力显著升高[80-81]。另有研究发现, 在几乎不表达ME2的胃癌细胞中, 其同工酶ME1的表达被显著上调, 用以补偿因ME2缺失导致的胞内NADPH水平下降[82]。

3.3 异柠檬酸脱氢酶(isocitrate dehydrogenase, IDH)

IDH有三种亚型, IDH1定位于细胞质; IDH2和IDH3定位于线粒体, 是三羧酸循环中的限速酶。IDH1和IDH2催化异柠檬酸氧化脱羧生成α-酮戊二酸和NADPH(图1); 而IDH3催化异柠檬酸生成α-酮戊二酸和NADH。

目前发现, IDH1在多种肿瘤细胞中高表达, 并与非小细胞肺癌及多种血液系统恶性肿瘤患者预后不良密切相关[83-84]。干涉IDH1表达会显著降低细胞NADPH水平, 并诱发肿瘤细胞凋亡[83]。在结直肠癌细胞中, IDH1的Lys224位点发生高乙酰化修饰可增强其活性, 且其乙酰化水平与远端转移和生存不良显著相关[85]。与IDH1类似, IDH2的表达在食管鳞状细胞癌、卵巢癌和肺癌等多种肿瘤细胞中也显著上调, 并与肿瘤的发生发展密切相关[86-88]。过表达IDH2可降低细胞内氧化压力, 促进肿瘤细胞增殖[89]。在B细胞淋巴瘤中, 去乙酰化酶SIRT3的缺失, 提高了IDH2在Lys413位点的乙酰化修饰水平。该修饰可以增强IDH2的酶活性, 促进肿瘤发生[90]。除

此之外, 近年还发现某些类型的肿瘤(如胶质瘤、急性髓系白血病、血管免疫母细胞淋巴瘤、软骨肉瘤和黑色素瘤等)细胞普遍携带*IDH1*和*IDH2*基因突变[91-92]。这些突变主要发生在与底物异柠檬酸结合的位点, 以*IDH1* Arg132、*IDH2* Arg140和Arg172突变最为常见[93]。令人意外的是, 这些突变体获得了新的催化功能, 即从原有催化异柠檬酸生成α-酮戊二酸转变为催化α-酮戊二酸还原生成2-羟基戊二酸, 而且这一体内罕见代谢物的产生具有显著的促肿瘤细胞增殖作用[93]。需要提及的是, 新的催化反应不但不生成, 反而是消耗了NADPH。这也提示, 在这些特殊类型的肿瘤细胞中, IDH1和IDH2对NADPH的生成并不重要, 反而是它们的突变体获得了驱动肿瘤发生发展的新功能。

4 结论与展望

代谢酶是肿瘤细胞异常代谢的直接驱动者, 但其本身也为肿瘤的治疗提供了宝贵的治疗靶点。目前已经有相当多的糖脂代谢关键酶抑制剂被开发出来并用于肿瘤的研究和治疗, 其中部分已进入临床试验阶段(表1)[94-110]。例如, FASN抑制剂Denifanstat已进入临床试验阶段, 被用于治疗三阴性乳腺癌(NCT03179904); G6PD抑制剂RRx-001也已进入临床试验阶段, 被用于治疗淋巴瘤(NCT02518958)和结直肠癌(NCT02096354)等, 这为发展更为有效的肿瘤治疗手段开辟了新的路径。然而, 这一研发过程仍然充满挑战。一是肿瘤细胞代谢的高度异质性。因组织来源、分化程度、定植环境等因素的差异, 肿瘤细胞将采用不同的代谢改变策略, 因此很难用简单的“特异性代谢模式”来定义所有肿瘤, 即使是对同一实体瘤内的肿瘤细胞。二是细胞代谢的高度可塑性。细胞代谢的复杂网络化赋予了其高度的补偿性, 这使得任何一种单一的靶点干预都很难取得长效作用。因此,

表1 糖脂代谢关键酶的抑制剂

Table 1 The inhibitors of key enzymes in glucose and lipid metabolism

酶 Enzymes	抑制剂 Inhibitors	肿瘤类型 Tumor type	临床试验编号 Clinical trials ID	参考文献 References
HK2	Lonidamine	Glioblastoma multiforme, breast cancer, lung cancer, ovarian cancer	N/A	[94]
	3-bromopyruvate	Leukemia, colorectal cancer, hepatocellular carcinoma	N/A	[95]
PFK1	3PO	Leukemia, melanoma, lung cancer, ovarian cancer	N/A	[96]
PKM2	Shikonin	Breast cancer, lung cancer, bladder cancer	NCT01968928	[97-98]
PGAM1	PGMI-004A	Leukemia, breast cancer, lung cancer, head and neck cancer	N/A	[26]
ACLY	SB204990	Leukemia, lung cancer, ovarian cancer, prostatic cancer	N/A	[99]
	BMS-303141	Hepatocellular carcinoma	N/A	[100]
ACC	ND-646	Lung cancer	N/A	[101]
FASN	Denifanstat	Breast cancer	NCT03179904	[102]
	Orlistat	Leukemia, melanoma, colon cancer	N/A	[103]
	C75	Breast cancer, ovarian cancer	N/A	[104]
CPT1	Etomoxir	Prostatic cancer, bladder cancer	N/A	[67-68]
G6PD	RRx-001	Multiple myeloma, colorectal cancer	NCT02518958 NCT02096354	[105-106]
	DHEA	Prostatic cancer, colon cancer	NCT01376349	[107]
ME1	ME1	Colon cancer	N/A	[108]
IDH1	Ivosidenib	Leukemia	NCT02074839 NCT04056910	[109]
IDH2	Enasidenib	Leukemia	NCT01915498	[110]

N/A: 无法获取。

N/A: not applicable.

通过单细胞代谢组学研究，深化对肿瘤细胞代谢异质性的理解，以及开展全细胞代谢通量分析，全面理解肿瘤细胞代谢的刚性需求与脆弱性，将是今后肿瘤细胞代谢领域研究的发展趋势。但无论如何，当前对肿瘤细胞代谢的研究正在如火如荼地进行中，相信未来以关键代谢酶为靶点的治疗策略会为肿瘤治疗提供更多的选择。

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