DOI: 10.11844/cjcb.2026.02.0002
中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(2): 250–266 CSTR: 32200.14.cjcb.2026.02.0002

· 实验室介绍 ·

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代谢酶在肿瘤发生发展中的非经典功能

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摘要 肿瘤细胞通过代谢重编程支持肿瘤的发生发展, 一方面代谢酶通过改变代谢途径提供物质与能量, 另一方面代谢酶还具有非代谢功能。代谢酶的非经典功能在肿瘤进展中扮演重要角色。该文系统综述了近年来代谢酶在表观遗传调控、信号转导及肿瘤微环境重塑中的新的作用机制。代谢酶可通过核转位、蛋白相互作用等多元方式, 直接调控基因表达、信号网络重塑及免疫应答, 这为开发靶向代谢酶非经典功能的精准治疗提供了新思路。

关键词 代谢酶; 非经典功能; 表观调控; 信号转导; 肿瘤微环境

Non-Canonical Function of Metabolic Enzyme in Tumor Progression

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收稿日期: 2025-11-13 接受日期: 2025-12-03
国科大杭州高等研究院专项资金(批准号: 2025HIAS-ZL014)资助的课题
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Received: November 13, 2025 Accepted: December 3, 2025
This work was supported by the Research Funds of Hangzhou Institute for Advanced Study, UCAS (Grant No.2025HIAS-ZL014)
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Abstract Metabolic reprogramming of tumor cells supports tumor initiation and progression. On one hand, metabolic enzymes provide materials and energy by altering metabolic pathways; on the other hand, they also exhibit non-metabolic functions. The non-canonical functions of metabolic enzymes play crucial roles in tumor progression. This review systematically summarizes key advances over the past decade, explaining novel mechanisms by which metabolic enzymes contribute to epigenetic regulation, signal transduction, and tumor microenvironment remodeling. Metabolic enzymes employ diverse mechanisms such as nuclear translocation, protein-protein interaction to directly modulate gene expression, signaling network rewiring, and immune responses. These findings provide a novel direction for developing precision oncology aimed at the non-canonical functions of metabolic enzymes.

Keywords metabolic enzymes; non-canonical functions; epigenetic regulation; signal transduction; tumor microenvironment

细胞代谢重编程是肿瘤的核心特征之一。肿瘤细胞通过改变代谢模式, 以适应其快速增殖、侵袭及转移过程中的生物能量与生物大分子的合成需求。为了应对各个阶段的不利因素, 肿瘤细胞通过代谢重编程支持肿瘤的存活。例如, 肿瘤细胞利用中心碳代谢, 即糖酵解途径、磷酸戊糖途径和三羧酸循环增强生物合成能力[1]; 通过加速糖酵解、三羧酸循环支持增殖[2]; 进入转移阶段后, 它们则通过增强细胞外基质相关合成代谢促进上皮–间充质转化并增强侵袭性[3]; 此外, 循环及休眠肿瘤细胞通过促进丙酮酸、乳酸和谷氨酰胺代谢来抵抗细胞凋亡、加速转移定植[4]。

近年来的研究发现, 代谢酶的功能远不止于催化经典的代谢反应, 其还能通过非经典途径直接参与表观遗传修饰、信号转导及肿瘤微环境调控, 从而影响肿瘤生物学行为[5-7]。尽管代谢酶的非经典功能日益受到关注, 但该领域认知仍呈现“碎片化”态势。大部分研究集中于单一代谢酶在特定肿瘤类型中的功能, 缺乏对其作用机制的系统性归纳, 未形成关于其如何协同驱动肿瘤恶性进展的整合视角。

因此, 系统解析代谢酶非经典功能的核心机制并归纳其分子调控规律, 可为推动该领域传统研究范式的转变及开发精准靶向干预策略奠定理论基础。这些发现不仅深化了我们对肿瘤代谢异常复杂性的认识, 也为克服传统靶向代谢治疗的局限性提供了全新视角。本文系统梳理了近十年代谢酶的非经典功能的研究进展, 重点阐述了其在表观遗传、信号转导和肿瘤微环境中的作用机制, 并展望了其作为新型治疗靶点的转化前景。

1 代谢酶参与的表观遗传调控

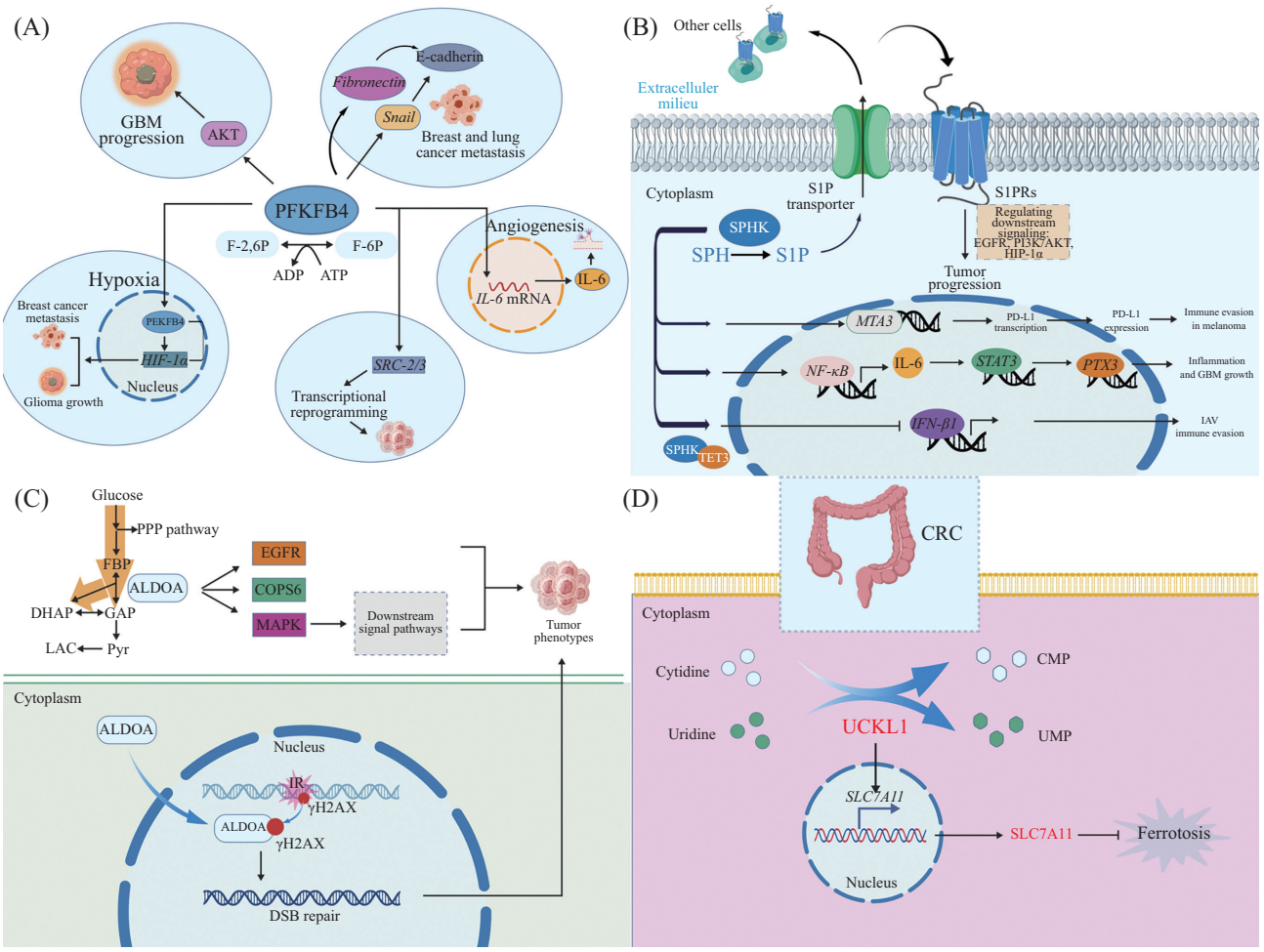
细胞代谢异常和表观遗传失调是肿瘤的特征之一, 共同构成了肿瘤发生发展的核心环节[2]。代谢酶不仅通过其经典代谢功能, 即催化反应产生代谢产物来间接调控表观遗传状态, 更能直接参与DNA甲基化、组蛋白修饰以及染色质结构重塑等过程, 从而在基因表达调控中发挥关键作用。

1.1 代谢酶参与基因表达调控

肿瘤的发生发展伴随原癌基因的异常表达, 深入探究代谢酶如何参与基因表达调控, 对于揭示肿瘤发生发展的新机制至关重要。近几年研究发现糖酵解途径中的代谢酶是核内转录调控的重要参与者。糖酵解途径的第二个限速酶6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶4(6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4, PFKFB4), 催化果糖-2,6-二磷酸的合成和降解, 通过增加糖酵解的代谢通量促进肺癌、乳腺癌转移[8-9]。研究表明, PFKFB4还能不依赖其代谢功能发挥影响肿瘤转移的作用: PFKFB4通过增强乳腺癌细胞中蜗牛家族转录抑制因子1(Snail family transcriptional repressor 1, Snail)表达和肺癌细胞中纤连蛋白的诱导作用来上调E-钙黏蛋白的表达, 从而促进肺癌细胞侵袭[10]。*PFKFB4*作为受缺氧诱导表达的关键基因在肿瘤转移中发挥重要作用, 缺氧条件能够诱导PFKFB4蛋白核转位, 在核内PFKFB4蛋白通过促进缺氧诱导因子1α(hypoxia inducible factor 1 alpha, HIF-1α)的激活促进乳腺癌远端转移和胶质母细胞瘤(glioblastoma, GBM)生长, 同时PFKFB4表达也受到HIF-1α调控, HIF-1α通过抑制E3泛素连接酶F-box/LRR重复蛋白7(F-box/LRR-repeat protein 7, FBXL7)表达从而增加PFKFB4蛋白的稳定性, 促进非小细胞肺癌(non-small cell lung cancer, NSCLC)生长[11-13]。在缺氧条件下, 肿瘤还通过促进新生血管的形成来缓解

其缺氧状态，研究发现PFKFB4也能通过上调白介素-6(interleukin-6, IL-6)的表达来促进血管生成[14]。除此之外，PFKFB4还能通过磷酸化类固醇受体共激活剂2/3(steroid receptor coactivator-2/3, *SRC-2/3*)增强其转录活性，通过SRC-2/3介导的转酮醇酶(transketolase, *TK*)和蛋白精氨酸甲基转移酶4(protein arginine methyltransferase 4, *PRMT4*/*CARM1*)表达上调驱动肺癌和乳腺癌转移[15-16](图1A)。

鞘脂类物质是细胞膜的重要组分之一，鞘脂代谢途径中的代谢酶也展现出调控基因表达的能力。鞘脂被催化生成鞘氨醇，鞘氨醇再被鞘氨醇激酶(sphingosine kinase, SPHK)催化生成鞘氨醇1-磷酸(sphingosine-1-phosphate, S1P)。一方面，SPHK通过其产物S1P发挥作用，S1P通过自分泌或旁分泌结合G蛋白偶联受体调节特定的信号通路如表皮生长因子受体(epidermal growth factor receptor, EGFR)、磷脂酰肌醇-3-激酶/AKT丝氨酸–苏氨酸蛋白激酶1(phosphoinositide 3-kinase/AKT serine-threonine kinase 1, PI3K/AKT)、S1P/HIF-1α等影响肿瘤进展[17-20]。另一方面，SPHK可以在转录水平调控基因表达影响抗肿瘤免疫和抗感染反应等。转移相关1家族成员3(metastasis associated 1 family member 3, *MTA3*)是SPHK1转录调控肿瘤程序性死亡1配体1(programmed cell death 1 ligand 1, PD-L1)的下游靶点，SPHK1通过MTA3/PD-L1轴促进黑色



A: PFKFB4在乳腺癌、肺癌、GBM和黑色素瘤中的非经典功能; B: SPHK在黑色素瘤、GBM和病毒感染过程中的非经典功能; C: ALDOA在胃癌、CRC和HCC中的非经典功能; D: UCKL1在CRC中的非经典功能。EMT: 上皮–间充质转化; GBM: 胶质母细胞瘤; HCC: 肝细胞癌; CRC: 结直肠癌; IAV: 甲型流感病毒。

A: non-canonical function of PFKFB4 in breast cancer, lung cancer, GBM and melanoma; B: non-canonical function of SPHK in melanoma, GBM and virus infection; C: non-canonical function of ALDOA in gastric cancer, CRC and HCC; D: non-canonical function of UCKL1 in CRC. EMT: epithelial-mesenchymal transition; GBM: glioblastoma; HCC: hepatocellular carcinoma; CRC: colorectal cancer; IAV: influenza A virus.

图1　代谢酶参与基因表达调控(图由BioGDP绘制)

Fig.1　Metabolic enzymes regulate gene expression (image created with BioGDP)

素瘤免疫逃逸[21]。SPHK1还可以通过核因子kappa B亚基1(nuclear factor kappa B subunit 1, NF-κB)/IL-6/信号转导和转录激活因子3(signal transducer and activator of transcription 3, STAT3)信号轴, 激活固有免疫重要组成部分五联毒素3(pentraxin 3, *PTX3*)的转录, 最终促进GBM细胞生长和炎症反应[22]。此外, SPHK2可通过抑制干扰素-β1(interferon-beta 1, *IFN-β1*)的转录影响宿主的细胞因子分泌[23](图1B)。

除了直接充当转录辅因子外, 代谢酶也能通过影响DNA损伤修复间接影响基因表达。果糖二磷酸醛缩酶A(aldolase, fructose-bisphosphate A, ALDOA)催化果糖-1,6-二磷酸生成甘油醛3-磷酸和二羟丙酮磷酸。研究表明ALDOA可以通过增加EGFR、AKT和激活丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)的磷酸化水平促进膀胱癌细胞侵袭[24]。ALDOA还可从细胞质转移到细胞核, 在DNA发生损伤时, 核内的ALDOA被招募至断裂位点, 与DNA双链断裂标志物H2A组蛋白家族成员X(H2AX variant histone, γ-H2AX)共定位[25]。机制上, ALDOA与DNA双链断裂修复的核心效应激酶DNA依赖蛋白激酶(DNA-dependent protein kinase, DNA-PK)和毛细血管扩张共济失调(ataxia telangiectasia mutated, ATM)相互作用, 增加DNA-PK的自磷酸化水平以激活激酶活性和提高DNA双链断裂修复能力; 此外, ALDOA还可通过ATM-Polo样激酶1(Polo-like kinase 1, PLK1)信号通路抑制DNA损伤所致的细胞周期阻滞, 从而多层面维持基因组稳定性并促进肿瘤细胞存活[26-28](图1C)。除此之外, 代谢酶也参与调控新型细胞死亡形式, 例如尿苷胞苷激酶样1(uridine-cytidine kinase like 1, UCKL1)通过催化尿苷和胞苷的磷酸化, 促进铁死亡经典阻滞蛋白溶质载体家族7成员11(solute carrier family 7 member 11, SLC7A11)的表达进而抑制肠癌细胞铁死亡[29](图1D)。

1.2 代谢酶参与组蛋白乙酰化调控

组蛋白乙酰化修饰在代谢酶的表观遗传调控中有重要体现, 组蛋白乙酰化修饰由组蛋白乙酰转移酶(histone acetyltransferase, HAT)和组蛋白去乙酰化酶(histone deacetylase, HDAC)调控, 并高度依赖乙酰辅酶A(acetyl coenzyme A, acetyl-CoA)的水平[30]。近年来研究发现, 代谢酶不仅通过代谢途径维持acetyl-CoA池稳态, 还可能通过非代谢功能直接调控组蛋白乙酰化状态。

丙酮酸脱氢酶(pyruvate dehydrogenase, PDH)是连接糖酵解和三羧酸循环的关键代谢酶, 催化丙酮酸脱羧生成acetyl-CoA[31]。研究发现在生长因子或线粒体应激等条件刺激下, PDH可由线粒体转位至细胞核, 影响与G_1-S进展和S期标志物表达相关组蛋白赖氨酸残基的乙酰化, 促进细胞周期从G_1期向S期过渡[32]。PDH的E1亚基alpha 1(pyruvate dehydrogenase E1 subunit alpha 1, PDHE1α)在DNA损伤应答中发挥重要作用, 经多聚ADP-核糖基化修饰后, PDHE1α快速募集到染色质, 通过在DNA双链断裂处局部产生acetyl-CoA, 重塑染色质以支持损伤修复并维持基因组稳定性[33-34]。

乳酸在组蛋白乙酰化调控中扮演关键角色。乳酸脱氢酶A(lactate dehydrogenase A, LDHA)通过核内代谢途径生成acetyl-CoA, 直接为组蛋白乙酰化提供必需的酰基供体[35-37]。ATP-柠檬酸激酶(ATP-citrate lyase, ACLY)作为连接糖代谢与acetyl-CoA合成的另一关键酶, 其活性也受乳酸影响[38-42]。乳酸通过ACLY依赖的形式改变染色质结构和组蛋白乙酰化, 促进营养匮乏条件下的GBM细胞存活和提高肠癌化疗的耐药性[42-43]。此外, 乳酸本身可作为内源性HDAC抑制剂, 在高糖酵解状态下积累并抑制HDAC相关蛋白的转录调节[44-45]。

4-羟基苯丙酮酸双加氧酶(4-hydroxyphenylpyruvate dioxygenase, HPD)是酪氨酸分解代谢中的关键酶, 催化羟苯丙酮酸生成尿黑酸和乙酰乙酸, 乙酰乙酸可被进一步催化生成acetyl-CoA。有研究发现, HPD不仅提升acetyl-CoA水平, 还通过肝激酶B1(liver kinase B1, LKB1)/AMP依赖的蛋白激酶[adenosine 5'-monophosphate (AMP)-activated protein kinase, AMPK]信号轴刺激HDAC10自细胞核至胞质转位。这两种机制共同增强了葡萄糖-6-磷酸脱氢酶(glucose 6-phosphate dehydrogenase, *G6PD*)的转录, 促进了肺癌细胞增殖和肿瘤生长[46]。

代谢酶参与的组蛋白乙酰化修饰包括三类: (1) 代谢酶或其代谢产物如acetyl-CoA、乳酸作为乙酰化反应的底物或调节因子; (2) 代谢酶直接调控HAT/HDAC活性或亚细胞定位; (3) 代谢酶通过影响HDAC功能间接重塑乙酰化状态。近年来, 代谢酶介导HDAC亚细胞定位变化和相关蛋白表达, 丰富了代谢酶参与组蛋白乙酰化修饰的方式。在转化医学方面, 尽管HDAC抑制剂已获批用于治疗部分血

液肿瘤, 但目前获批的多数为广谱抑制剂, 对实体瘤疗效有限(表1)。因此, 以特定代谢酶及其驱动的乙酰化为靶点开发精准疗法, 有望为实体瘤治疗开辟新路径。

1.3 代谢酶组蛋白乳酰化修饰

组蛋白乳酰化(histone lactylation)是近年来发现的一种新型表观遗传修饰, 由乳酸衍生的乳酰基团共价连接于组蛋白赖氨酸残基所介导。这一发现将细胞代谢与基因转录调控更为直接地联系起来, 而代谢酶在其中扮演了核心角色。

近期研究揭示了乳酸参与表观遗传调控的另一机制, 乙酰辅酶A合成酶2(acetyl-CoA synthetase 2, ACSS2)可直接充当乳酰辅酶A合成酶, 催化乳酸生成乳酰辅酶A(lactyl-CoA); 同时ACSS2能与赖氨酸乙酰转移酶2A(lysine acetyltransferase 2A, KAT2A)结合, 并引导其将乳酰基团转移至组蛋白赖氨酸残基, 催化组蛋白乳酰化修饰。 KAT2A通过乳酰化组蛋白H3, 上调Wnt/β-连环蛋白(Wnt/β-catenin)、NF-κB和PD-L1表达, 促进神经胶质瘤的免疫逃逸[54]。

除乳酰化修饰外, ACSS2在不同肿瘤背景下展现出广泛的表观遗传调控作用。ACSS2促进过氧化物酶体增殖物激活受体δ(peroxisome proliferator-activated receptor δ, *PPARD*)启动子区域H3K27位点的乙酰化, 促进支链氨基酸转氨酶1(branched-chain amino acid transaminase 1, *BCAT1*)转录和支链氨基酸分解代谢, 进而增强胰腺癌细胞的增殖和侵袭能力[55]。在胰腺神经内分泌肿瘤的免疫逃逸过程中, ACSS2通过乙酰化组蛋白H3/H4招募凋亡拮抗转录因子(apoptosis antagonizing transcription factor, AATF)来调节Fas配体(Fas ligand, *FasL*)转录, 驱动可溶性FasL分泌, 进而通过结合$CD8^+$ T细胞的Fas受体激活半胱天冬酶-8/3(Caspase-8/3)级联反应, 触发T细胞凋亡[56]。在果糖或乙酸盐环境下, Nogo-B受体(Nogo-B receptor, NgBR)可通过激活AKT-SREBP1(sterol regulatory element-binding protein 1)信号通路诱导ACSS2表达, 增强ACSS2利用果糖代谢产物合成acetyl-CoA的能力。ACSS2通过增强原癌基因*MYCN*(MYCN proto-oncogene, BHLH transcription factor)转录促进神经母细胞瘤生长[57]。

综上所述, 以ACSS2为代表的代谢酶通过催化lactyl-CoA生成, 直接驱动组蛋白乳酰化修饰, 将高糖酵解肿瘤状态下的乳酸积累与特定的免疫及生长相关基因转录程序相偶联。这不仅揭示了代谢酶在表观遗传领域的一种全新非经典功能, 也为理解肿瘤代谢与免疫微环境互作提供了新的分子视角。

1.4 代谢酶参与甲基化调控

代谢酶不仅通过代谢产物影响表观遗传状态, 更能以非代谢的形式直接调控DNA、RNA和组蛋白的甲基化修饰。DNA甲基转移酶(DNA methyltransferases, DNMT)催化*S*-腺苷甲硫氨酸(*S*-adenosyl methionine, SAM)产生, DNMT在DNA甲基化过程中扮演了双重角色: 一方面参与DNA甲基化修饰, 引起染色质结构的变化, 精准调控DNA甲基化进程; 另一方面, 其代谢产物SAM是不可或缺的甲基供体[58]。

表1 已获批及在研的HDAC/HAT抑制剂

Table 1 Approved and investigational HDAC/HAT inhibitors

类别 Category	名称 Name	疾病 Disease	临床试验 Clinical trail
HDAC inhibitor	Vorinostat (SAHA)	Cutaneous T-cell lymphoma[47]	FDA approved
	Romidepsin	T-cell lymphoma[48]	FDA approved
	Belinostat	Peripheral T-cell lymphoma[49]	FDA approved
	Panobinostat (Farydak)	Relapsed or refractory multiple myeloma after immunomodulatory drugs and proteasome inhibitors, combined with bortezomib and dexamethasone for multiple myeloma patients[50]	FDA approved
	Givinostat	Duchenne muscular dystrophy[51]	Phase II/III
	Abexinostat	GBM, renal cell carcinoma, and non-Hodgkin's lymphoma[52]	Phase III
HAT inhibitor	Curcumin	Liver cancer[53]	/

HDAC: 组蛋白去乙酰化酶; HAT: 组蛋白乙酰转移酶; GBM: 胶质母细胞瘤。"/"表示该抑制剂未进行临床试验或未明确报道临床试验阶段, 或处于临床前研究阶段。

HDAC: histone deacetylase; HAT: histone acetyltransferase; GBM: glioblastoma. "/" indicates that no clinical trial has been conducted or the clinical trial stage has not been explicitly reported for this inhibitor, or it is in the preclinical research stage.

磷酸核糖焦磷酸合成酶2(phosphoribosyl pyrophosphate synthetase 2, PRPS2)参与嘌呤核苷酸合成限速步骤, 催化D-核糖-5-磷酸产生5-磷酸核糖-α-1-焦磷酸。PRPS2通过酶活性依赖与非依赖的双重机制驱动RNA m^{6}A甲基化。一方面, PRPS2通过促进嘌呤合成代谢, 来对抗由产物ADP或GDP引发的变构反馈抑制, 防止自身活性下调, 维持SAM生物合成所需的过量ATP供应; 另一方面, PRPS2还能直接结合并稳定蛋氨酸腺苷转移酶2A(methionine adenosyltransferase 2A, MAT2A), 促进ATP利用和SAM生成, 进而通过甲基转移酶复合物WTAP(WT1 associated protein)/METTL3(methyltransferase 3)/METTL14(methyltransferase 14)促进m^{6}A甲基化, 最终促进肺癌发生和转移[59]。

除此之外, 代谢酶还可以通过蛋白质相互作用的形式直接调控组蛋白甲基化。活性氧(reactive oxygen species, ROS)累积能驱动LDHA核转位, 进而触发DOT1样组蛋白赖氨酸甲基转移酶(DOT1 like histone lysine methyltransferase, DOT1L)介导的组蛋白H3第79位赖氨酸(H3K79)高甲基化, 从而激活抗氧化反应和Wnt信号通路, 调节细胞氧化还原平衡[60], 最终促进GBM细胞增殖和肺腺癌的血管生成[61-62]。

2 代谢酶参与的信号转导调控

代谢酶的功能已拓展至其经典代谢角色之外, 其成为细胞信号转导网络中不可或缺的调控中枢[63], 代谢酶通过蛋白相互作用、翻译后修饰及作为RNA结合蛋白(RNA binding protein, RBP)调控翻译等机制, 直接参与信号网络的精密调控。

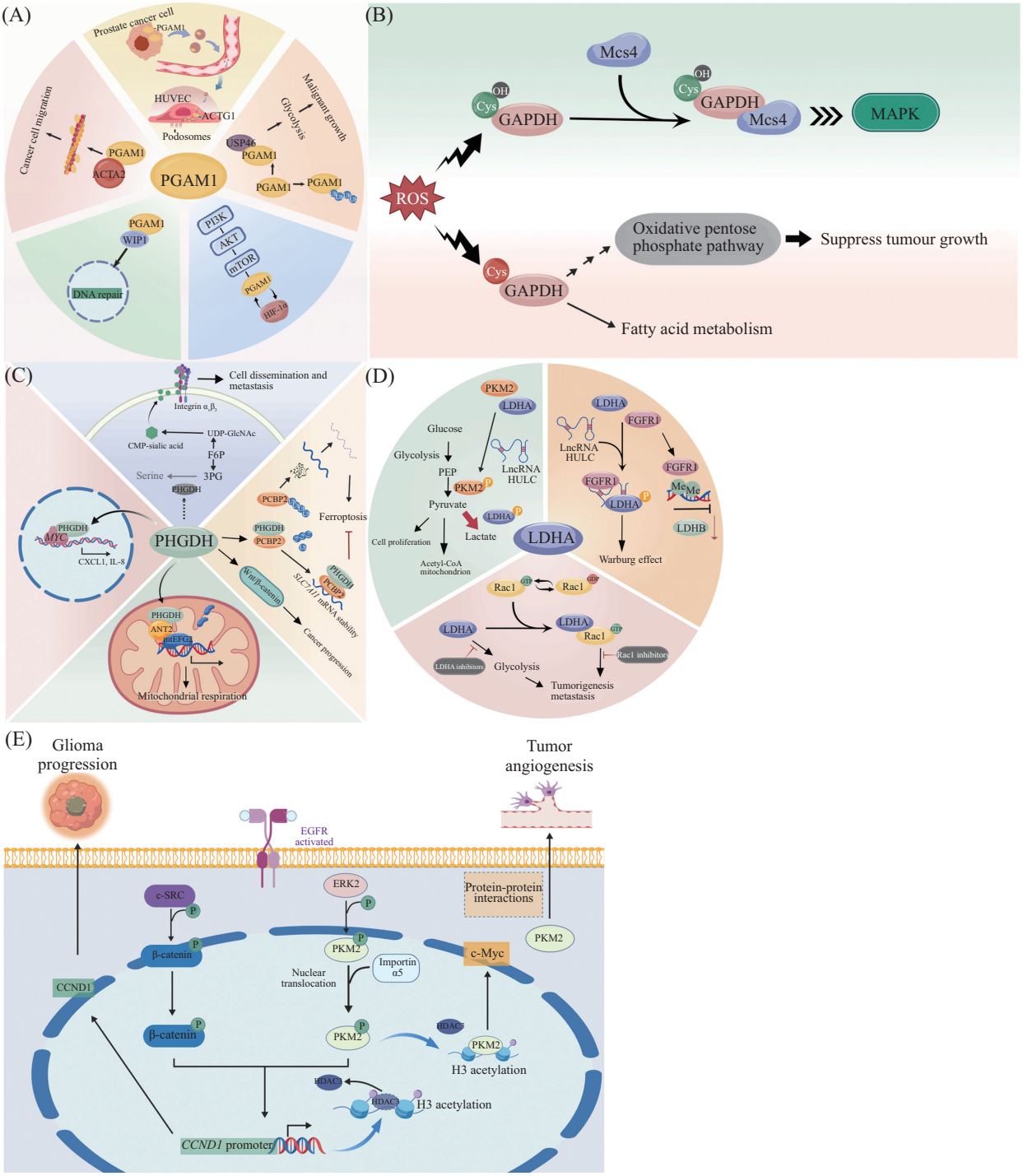
2.1 代谢酶通过蛋白相互作用参与信号调控

代谢酶通过精密的蛋白质相互作用, 直接调控与肿瘤发生发展相关的关键信号通路, 这一机制已成为肿瘤代谢领域的研究前沿。

作为糖酵解通路中的关键酶, 磷酸甘油酸变位酶1(phosphoglycerate mutase 1, PGAM1)催化3-磷酸甘油酸和2-磷酸甘油酸的相互转化。PGAM1通过与不同配体相互作用发挥重要功能: 直接参与DNA损伤修复以维持基因组稳定性或调控关键致癌信号通路[64](图2A)。PGAM1可以与α-平滑肌肌动蛋白2(actin alpha 2 smooth muscle, ACTA2)相互作用促进乳腺癌转移[65]。近年来的研究发现PGAM1通过外泌体进行细胞间通讯, 前列腺细胞来源的外泌体包裹的PGAM1可被传递到人脐静脉内皮细胞, 与γ-肌动蛋白(actin gamma 1, ACTG1)结合促进周围侵足形成和新生血管生成, PGAM1具有成为前列腺癌转移液体活检标志物的潜力[66]。在胰腺癌中, PGAM1受PI3K/AKT/哺乳动物雷帕霉素靶蛋白(the mammalian mechanistic target of rapamycin, mTOR)信号调控, 并与HIF-1α存在正反馈调节[67]。

甘油醛-3-磷酸脱氢酶(glyceraldehyde-3-phosphate dehydrogenase, GAPDH)在氧化应激信号中发挥关键作用。*GAPDH*催化3-磷酸甘油醛生成D-甘油酸1,3-二磷酸, 被归类为“管家基因”。其活性位点半胱氨酸残基对过氧化氢极为敏感, 氧化修饰会导致其快速失活。当氧化应激关闭此开关时, 肿瘤生长被抑制, 而携带抗氧化突变的GAPDH, 虽保留了催化活性, 却失去了驱动氧化戊糖磷酸途径的能力, 转而启动脂肪酸代谢作为代偿通路[68]。GAPDH半胱氨酸残基被氧化后, 其与mcs4反应调节因子(response regulator mcs4, Mcs4)的相互作用得以增强, 从而将细胞的代谢状态与MAPK信号级联通路偶联起来[69](图2B)。

丝氨酸合成通路的关键酶磷酸甘油酸脱氢酶(phosphoglycerate dehydrogenase, PHGDH)通过其亚细胞定位的多样性及蛋白稳定性的精密调控执行非经典功能。PHGDH在肿瘤中高表达, 催化3-磷酸甘油酸生成3-磷酸羟基丙酮酸。PHGDH在肿瘤细胞中的异质性表达赋予了特定细胞亚群关键的代谢可塑性, 这些细胞通过PHGDH介导的丝氨酸合成代谢产生α-酮戊二酸, 进而促进整合素$\alpha_v\beta_3$发生特定糖基化修饰, 增强肿瘤细胞的侵袭和定植能力[70]。PHGDH的功能多样性与其在细胞内的动态分布密切相关: 在肝癌细胞中PHGDH可易位至线粒体膜, 与腺嘌呤核苷酸转位酶2(adenine nucleotide translocase 2, ANT2)相互作用, 通过招募线粒体伸长因子G2(mitochondrial elongation factors G2, mtEFG2)提升线粒体核糖体循环效率, 从而促进呼吸链复合物的表达和线粒体呼吸[71]。PHGDH的细胞核定位也体现了它的非代谢功能。研究表明核内PHGDH以非酶活依赖的形式结合原癌基因*MYC*(MYC proto-oncogene, bHLH transcription factor)并激活其转录, 驱动趋化因子C-X-C基序趋化因子配体1(C-X-C motif chemokine ligand 1, CXCL1)和白介素-8(interleukin-8, IL-8)表达, 通过招募中性粒细胞和肿瘤相关巨噬细胞并促进其浸润来重塑肝癌



A: PGAM1介导的转移调控; B: GAPDH感知氧化应激; C: PHGDH调控代谢与铁死亡; D: LDHA促进肿瘤细胞侵袭; E: PKM2介导的转录与血管生成调控。PDAC: 胰腺导管腺癌; HUVEC: 人脐静脉内皮细胞。

A: PGAM1-mediated metastasis; B: GAPDH senses oxidative stress; C: PHGDH regulates metabolism and ferroptosis; D: LDHA promotes tumor cell invasion; E: PKM2-mediated transcription and angiogenesis. PDAC: pancreatic ductal adenocarcinoma; HUVEC: human umbilical vein endothelial cells.

图2 代谢酶通过蛋白相互作用参与信号调控(图由BioGDP绘制)

Fig.2 Metabolic enzymes regulate signaling through protein-protein interactions (image created with BioGDP)

细胞微环境[72]。此外, PHGDH还能通过结合多聚胞嘧啶结合蛋白2[poly(rC) binding protein 2, PCBP2]来稳定*SLC7A11*的mRNA并防止其降解, 进而抑制铁死亡[73]和促进膀胱癌进展[74]。然而, PHGDH的蛋白稳定性调控也是影响其功能的关键机制, 多种E3泛素连接酶对其表现出双向调控机制: RING指和WD重复结

构域3(RING finger and WD repeat domain 3, RFWD3)和RING指蛋白5(RING finger protein 5, RNF5)分别通过直接与PHGDH相互作用阻止或促进其泛素化降解,从而实现对PHGDH的双向调控[75-76]。Cullin 4A-RING E3泛素连接酶(Cullin 4A-RING E3 ubiquitin ligase)以Cullin 4A为支架蛋白, 并与DNA损伤结合蛋白1(DNA damage-binding protein 1, DDB1)等组分共同构成E3泛素连接酶复合物(常被统称为DDB1-CUL4 E3泛素连接酶复合物), 该复合物可介导PHGDH的第146位赖氨酸单泛素化修饰驱动结直肠癌转移[77-78](图2C)。

代谢酶与关键信号蛋白的相互作用还能被长链非编码RNA精确调控, 形成复杂的调控网络。WANG等[79]发现肝癌中高度上调的长链非编码RNA HULC能够直接结合LDHA和丙酮酸激酶M2(pyruvate kinase M2, PKM2), 增强二者与成纤维细胞生长因子受体1(fibroblast growth factor receptor 1, FGFR1)的相互作用并促进其磷酸化, 通过提高有氧糖酵解水平来促进肝癌细胞增殖。除了之前的表观遗传调控外, LDHA在信号转导中同样活跃[80]。研究证实FGFR1通过与乳酸脱氢酶同工酶发生直接相互作用, 从而调控前列腺癌的能量代谢重编程[81]。尤为重要的是, LDHA可直接激活Rac家族小GTP酶1(Rac family small GTPase 1, Rac1)[82], LDHA与活化形式的Rac1-GTP结合, 通过“分子支架”作用维持其活性状态促进细胞骨架重塑,从而促进乳腺癌生长和转移[83](图2D)。

PKM2作为糖酵解的关键调控节点, 是代谢酶行使多维度的非经典功能的典范[84](图2E)。当细胞膜上的EGFR被激活时, 细胞外信号调节激酶2(extracellular signal-regulated kinase 2, ERK2)直接结合并磷酸化PKM2, 促进PKM2与核转运蛋白α5(importin α5)的相互作用并将PKM2转运至细胞核[85]。在核内, PKM2的K433与被非受体酪氨酸激酶磷酸化的β-catenin的Y333位点结合。这一相互作用导致其被招募到细胞周期蛋白D1(Cyclin D1, *CCND1*)的启动子, 并通过拮抗HDAC3的功能促进组蛋白H3乙酰化和CCND1表达, 最终影响GBM进展[86]。PKM2也可以直接结合并磷酸化H3, 拮抗HDAC3的功能从而促进H3的乙酰化,影响CCND1和c-Myc(由原癌基因*MYC*编码)表达, 最终促进脑肿瘤发生[87]。PKM2还能以多种形式的蛋白相互作用参与肿瘤血管生成。FOX转录因子家族蛋白FOXM1D(forkhead box M1D)通过与PKM2四聚体相互作用并组装成异二聚体来抑制PKM2的代谢活性。同时, FOXM1D与PKM2和NF-κB相互作用, 在核转运蛋白帮助下转入核内, 随后PKM2和NF-κB促进血管内皮生长因子A(vascular endothelial growth factor A, *VEGFA*)转录和外泌体分泌, 最终促进结直肠癌的血管生成[88]。

综上所述, 代谢酶通过蛋白质相互作用参与信号转导, 其机制可被归纳为以下几个层面。(1) 亚细胞定位改变: 被招募至细胞核内, 直接调控基因转录与组蛋白修饰; 或进入线粒体, 影响线粒体基因组编码蛋白的表达与能量代谢; (2) 分子支架与竞争性抑制: 促进或竞争性抑制关键信号蛋白的相互作用,从而精确调控通路活性; (3) 细胞间信使: 通过外泌体等囊泡在细胞间传递, 将代谢信号传递至微环境,重塑细胞间通讯。这些发现为靶向肿瘤代谢–信号交叉网络的治疗策略提供了理论基础。

2.2 代谢酶介导翻译后修饰参与信号调控

质谱技术的发展推进了蛋白修饰网络的解析,代谢酶被发现可以具备独立的激酶或磷酸酶活性,直接催化关键信号蛋白或组蛋白的翻译后修饰。一部分代谢酶展现出蛋白激酶或蛋白磷酸酶活性, 介导蛋白的磷酸化或去磷酸化。果糖1,6-二磷酸酶1(fructose-1,6-bisphosphatase 1, FBP1)在糖异生途径中催化果糖1,6-二磷酸水解为果糖-6-磷酸。FBP1通过去磷酸化组蛋白H3来抑制过氧化物酶体增殖物激活受体α(peroxisome proliferator activated receptor alpha, PPARα)介导的脂肪酸氧化及相关基因转录[89-90]。FBP1还能直接作用于胞质信号通路: FBP1通过催化人核因子κB抑制蛋白α(NF-κB inhibitor alpha, IκBα)第32和36位丝氨酸(S32/36)的去磷酸化抑制NF-κB激活, 增加结直肠癌细胞对炎症刺激的敏感性[91-92]。

部分代谢酶则进化出了独立的蛋白激酶活性,从而将其对代谢状态的感知与信号转导功能相偶联[93]。酮己激酶A(ketohexo kinase A, KHK-A)是果糖代谢途径中第一个限速酶, 催化果糖生成1-磷酸果糖。KHK-A分别受氧化应激或底物果糖刺激, 磷酸化p62(sequestosome 1)、酪氨酸3-单加氧酶/色氨酸5-单加氧酶激活蛋白eta(tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein eta, YWHAH)或PKM2, 促进HCC发生、乳腺癌转移或肠癌转移[94-96]。含有己糖激酶结构域的蛋白1(hexokinase domain-containing protein 1, HKDC1)进入细胞核后, 可发挥蛋白激酶的功能, 通过磷酸

化RB结合蛋白5(RB binding protein 5, histone lysine methyltransferase complex subunit, RBBP5)增强组蛋白赖氨酸甲基转移酶2A(lysine methyltransferase 2A, KMT2A/MLL1)复合物的活性, 促进有丝分裂相关基因表达和肝细胞癌增殖[97]。丙酮酸脱氢酶激酶4(pyruvate dehydrogenase kinase 4, PDK4)可以磷酸化PDHE1α并在调节氧化磷酸化驱动的ATP产生中发挥作用, 近年来有文章报道其非经典的独立激酶功能[98], PDK4通过磷酸化小G蛋白家族蛋白胞裂蛋白2(septin 2, SEPT2)促进肺癌细胞生长[99]。UDP-*N*-乙酰葡萄糖胺焦磷酸化酶1(UDP-*N*-acetylglucosamine pyrophosphorylase 1, UAP1)也被报道通过焦磷酸化干扰素调节因子3(interferon regulatory factor 3, IRF3)的386位点促进肺癌细胞的I型干扰素信号通路应答[99]。

代谢酶介导翻译后修饰已成为其行使非经典功能的核心机制之一。其主要特征归纳如下。(1) 催化功能的多样性: 代谢酶可获得激酶或磷酸酶活性, 直接修饰信号蛋白或组蛋白; (2) 信号转导的直接性: 通过催化关键的翻译后修饰, 代谢酶能够绕过传统的信号级联, 快速精准地调控下游通路; (3) 生理病理意义的普适性: 从调控细胞代谢到影响免疫应答, 这一机制在多种生命过程和疾病状态发挥重要作用。

2.3 代谢酶作为RNA结合蛋白参与信号调控

代谢酶除通过蛋白质相互作用及翻译后修饰调控信号通路之外, 其作为RNA结合蛋白直接调控RNA代谢与翻译的非经典功能, 正受到越来越多的关注。这一机制紧密连接了细胞代谢与基因表达[100]。

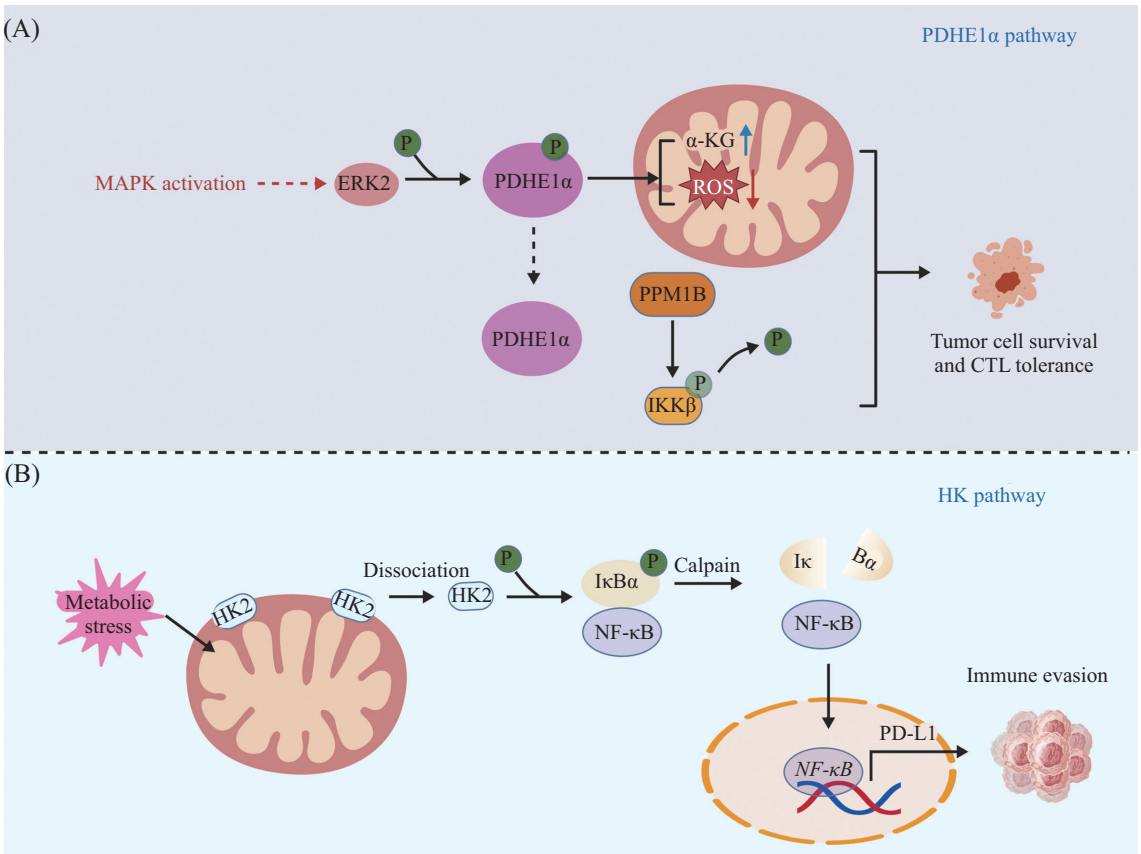
烯醇化酶1(enolase1, ENO1)是诠释代谢酶多重RNA结合功能的典型案例, ENO1在糖酵解途径中催化2-磷酸甘油酸和磷酸烯醇丙酮酸的可逆转化, 且在进化上保守地具备RNA结合能力。ENO1的酶活性受RNA与代谢底物的竞争性抑制, 而ENO1自身的乙酰化修饰能调控这一过程, 进而影响小鼠胚胎干细胞代谢重编程[101]。在mRNA稳定性调控方面, ENO1招募转录因子CCR4-NOT转录复合体亚基6(CCR4-NOT transcription complex subunit 6, CNOT6)至铁调蛋白1(iron regulatory protein 1, *IRP1*) mRNA的5′非翻译区(5′ untranslated region, 5′ UTR), 促进*IRP1* mRNA降解, 进而抑制IRP1-线粒体蛋白1(mitofusin 1, Mfn1)介导的肝癌细胞铁死亡[102]。同时ENO1也直接调控mRNA翻译效率, 通过结合Yes关联蛋白1(Yes-associated protein 1, *YAP1*) mRNA上的特定序列元件促进其翻译, 进而驱动异常的花生四烯酸代谢和促进肝癌生长[103]。在胃癌中, ENO1结合SRY-盒转录因子9(SRY-box transcription factor 9, *SOX9*)、*VEGFA*、G蛋白偶联受体C组5成员A(G protein-coupled receptor class C group 5 member A, *GPRC5A*)和*MCL1*(MCL1 apoptosis regulator, BCL2 family member)的mRNA并维持其表达, 形成广泛的促癌网络[104-106]。

PKM2还能作为RNA结合蛋白直接调控翻译过程[107-108]。研究发现, PKM2通过与核糖体结合, 并特异性结合编码赖氨酸/谷氨酸富集蛋白的mRNA的3′ UTR, 从而导致翻译停滞[109], 这直接提供了代谢状态调控特定蛋白质合成的直接证据。其他代谢酶同样广泛参与转录后调控, 影响从肿瘤转移到免疫应答等多种生命活动。GAPDH被证实可结合干扰素γ(interferon gamma, *IFN-γ*)的mRNA并抑制其翻译从而调节效应T细胞功能[110]。类似地, 其通过结合在集落刺激因子1(colony stimulating factor 1, *CSF-1*) mRNA的3′ UTR并阻止其降解导致卵巢癌转移[111]。在酵母中, GAPDH作为RBP, 通过与脂肪酸合酶1(fatty acid synthase 1, *FAS1*) mRNA相互作用调控其周期性表达, 确保细胞分裂的正常进行[112]。乌头酸酶1(aconitase 1, ACO1)则揭示了代谢酶在天然免疫中的核心地位: 其受MAPK家族成员p38γ/δ调控, 通过结合丝裂原活化蛋白激酶8(mitogen-activated protein kinase kinase kinase 8, *MAP3K8*/*TPL2*)的3′ UTR来降低髓系细胞中TPL2的蛋白表达水平[113-114]。

综上所述, 代谢酶作为RNA结合蛋白构成了一个庞大而精密的转录后调控网络, 其作用机制主要包括以下几个方面。(1) 直接结合mRNA: 通过影响其稳定性或翻译效率, 精确调控癌或抑癌基因的表达水平; (2) 受非编码RNA调控: 形成复杂的反馈与前馈回路, 动态响应细胞状态; (3) 整合多重信号: 作为分子平台, 耦合代谢状态、信号通路与基因表达输出。这一研究领域不仅极大拓展了对代谢酶的非经典功能的认知, 更提示了靶向特定“代谢酶-RNA”相互作用可能为癌症治疗开辟全新的策略方向。

3 代谢酶通过非经典功能调控肿瘤微环境

肿瘤微环境的高度异质性决定了其细胞组成、代谢状态及免疫特征的复杂性, 代谢酶通过其非经典功能, 在重塑免疫抑制性微环境中发挥了核心作



A: PDHE1α通过亚细胞转位解除NF-κB抑制, 促进肺癌免疫耐受; B: HK2通过降解IκBα激活NF-κB信号驱动胶质母细胞瘤免疫逃逸。

A: PDHE1α promotes lung cancer immune tolerance by subcellular translocation and depressing NF-κB; B: HK2 drives glioblastoma immune evasion by degrading IκBα and activating NF-κB signaling.

图3 代谢酶通过非经典功能调控肿瘤微环境(图由BioGDP绘制)

Fig.3 Metabolic enzymes regulate tumor microenvironment through noncanonical functions (image created with BioGDP)

用[115-116]。

代谢酶通过调控关键免疫信号通路, 直接影响肿瘤细胞的免疫原性及免疫细胞功能[117]。通常情况下, PDHE1α在细胞质中通过促进Mg^{2+}/Mn^{2+}依赖性蛋白磷酸酶1B(protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1B, PPM1B)对IκB激酶β(inhibitor of nuclear factor kappa B kinase subunit beta, IKKβ)的去磷酸化抑制NF-κB信号通路。在MAPK信号激活情况下, ERK2会磷酸化胞质内PDHE1α的S327位点, 促使PDHE1α转位至线粒体。PDHE1α从胞质中移出, 解除了其对NF-κB信号通路的抑制作用。同时, 线粒体中的PDHE1α累积会提升α-酮戊二酸的含量并促进炎症因子刺激后的ROS清除。NF-κB的活化和ROS的清除共同增强了肺癌细胞对细胞毒性T细胞(cytotoxic T lymphocytes, CTLs)的耐受性, 促进了肿瘤的免疫逃逸并提高了抗程序性细胞死亡蛋白1(programmed cell death protein 1, PD-1)治疗的耐药性[118](图3A)。除了线粒体代谢酶外, 定位在线粒体外膜的糖酵解酶也具备独特的免疫调控功能。己糖激酶2(hexokinase 2, HK2)是催化糖酵解第一步的关键酶, 催化葡萄糖生成6-磷酸葡萄糖[119]。在过量产物堆积等代谢压力下, HK2可从线粒体外膜脱落进入细胞质, 结合IκBα并促进其降解, 介导NF-κB核转位并促进PD-L1表达, 从而促进神经胶质瘤的免疫逃逸[120](图3B)。

代谢酶及其产物还能通过其非经典功能, 以转录调控方式建立免疫抑制程序。细胞表面核苷酸酶(5'-nucleotidase, NT5E/CD73)可催化细胞外AMP脱磷酸生成腺苷, 是腺苷生成的关键限速酶。通常CD73在细胞表面的异常表达导致腺苷在细胞外累积, 从而抑制淋巴细胞浸润[121-124]。CD73还通过非经典功能调节胰腺癌的免疫抑制微环境: 通过腺苷受体A2A(adenosine A2A receptor, ADORA2A)信号激活p38(MAPK14)-信号转导与转录激活因子1(signal

transducer and activator of transcription 1, STAT1)通路, 上调C-C基序趋化因子配体5(C-C motif chemokine ligand 5, *CCL5*)转录水平, 以肿瘤自分泌的方式招募调节性T细胞[125]。代谢物也可直接充当信号分子, 脂肪酸氧化来源的acetyl-CoA通过参与NF-κB转录因子复合物的关键亚基p65(由*RELA*编码)的乙酰化促进免疫检查点*CD47*的转录, 进而驱动GBM侵袭和免疫逃逸[126]。叶酸循环中的亚甲基四氢叶酸脱氢酶2[methylenetetrahydrofolate dehydrogenase (NADP$^+$ dependent) 2, methenyltetrahydrofolate cyclohydrolase, MTHFD2]则依赖其产物尿苷 5'-二磷酸-*N*-乙酰氨基葡萄糖(uridine diphosphate-*N*-acetylglucosamine, UDP-GlcNAc)发挥非代谢功能[127], 通过促进*MYC*的*O*-连接β-*N*-乙酰氨基葡萄糖(*O*-GlcNAc)糖基化修饰上调*PD-L1*的转录表达, 导致胰腺癌的肿瘤发生和免疫逃逸[128], 这一发现首次揭示了MTHFD2在细胞信号转导和癌症生物学中的非代谢作用。

代谢酶还可作为细胞间信使, 通过外泌体途径远程重塑肿瘤微环境[129], PKM2被发现在其中扮演关键角色[130]。一方面, 肝癌来源的外泌体PKM2经SUMO(SUMOylation)化修饰后, 通过C-C基序趋化因子配体1(C-C motif chemokine ligand 1, CCL1)/C-C基序趋化因子受体8(C-C motif chemokine receptor 8, CCR8)轴依赖的方式被单核细胞摄取, 进而诱导STAT3磷酸化及转录重编程, 驱动巨噬细胞分化[131]。另一方面,在缺氧条件下, NSCLC细胞会分泌包被PKM2的外泌体。这些外泌体被肿瘤相关成纤维细胞(cancer associated fibroblasts, CAFs)摄取后, 能中和顺铂诱导的ROS及还原性代谢物, 促进CAFs的代谢适应, 最终增强肿瘤化疗耐药[132]。

综上所述, 代谢酶通过多元化的非经典机制深刻影响肿瘤免疫微环境, 其主要途径包括以下方面。(1) 代谢物信号转导: 代谢产物作为信号分子, 通过修饰转录因子或染色质直接调控免疫相关基因表达; (2) 亚细胞定位转换: 代谢酶通过改变其细胞定位, 获得调控NF-κB等关键信号通路的新功能; (3) 外泌体介导的远程通讯: 代谢酶通过外泌体在细胞间传递, 实现对免疫细胞和基质细胞的代谢重编程与功能调控。这些发现不仅揭示了肿瘤免疫逃逸的新机制, 更提示了我们靶向代谢酶的非经典功能, 尤其是其介导的免疫抑制通路, 与现有免疫疗法联用, 有望克服肿瘤异质性及治疗耐药提供全新的联合治疗策略。

4 代谢酶通过非经典功能治疗肿瘤

针对代谢酶的非经典功能的直接靶向策略, 旨在特异性干扰其经由蛋白质相互作用、非经典催化活性或异常亚细胞定位所介导的促癌功能, 同时尽可能保留其基本代谢活性以降低毒性。

基于对代谢酶的非经典功能的深入了解, 开发能够特异性靶向其蛋白质相互作用界面的抑制剂, 已成为克服肿瘤耐药与转移的重要治疗策略[133]。在肺腺癌中, 针对PGAM1的新型变构抑制剂HKB99, 可以通过结合PGAM1的变构位点, 有效破坏其与Janus激酶2(Janus kinase 2, JAK2)和STAT3之间的相互作用, 成功逆转肿瘤细胞对第一代和第三代EGFR酪氨酸激酶抑制剂(EGFR tyrosine kinase inhibitors, EGFR-TKI)厄洛替尼和奥西替尼的获得性耐药[134]。进一步研究证实, HKB99还通过变构调节抑制PGAM1的构象变化及其与α-平滑肌肌动蛋白1(actin alpha 1, skeletal muscle, ACTA1)的相互作用, 同时靶向其代谢活性和非代谢功能, 提供克服NSCLC耐药的双重机制[135]。基于以往对LDHA和Rac1相互作用在肿瘤进展中的报道, LIU等[83]发现LDHA的NADH竞争性抑制剂FX11和Rac1抑制剂NSC23766虽均可单独抑制肿瘤, 但二者联用能展现出更强的协同肿瘤抑制作用。除了小分子抑制剂外, 靶向蛋白降解策略也取得重要进展。例如, 一种新型"分子胶"可增强PHGDH和DDB1-CUL4 E3泛素连接酶复合物的相互作用, 从而触发PHGDH的泛素化降解, 显著抑制结直肠癌干性[136]。类似地, ZHANG等[76]采用虚拟筛选技术, 将洛米他派鉴定为RFWD3-PHGDH相互作用的特异性抑制剂, 该化合物与顺铂联合使用在骨肉瘤治疗中表现出显著的协同抗肿瘤作用。此外, 肽类药物也展现出独特优势。有研究设计了一种特异性多肽, 其序列源自胰岛素诱导基因1/2(insulin induced gene 1/2, *Insig1/2*)的第一环区。该多肽通过竞争性结合被AKT磷酸化的磷酸烯醇丙酮酸羧激酶1(phosphoenolpyruvate carboxykinase 1, PCK1), 阻断PCK1与Insig1/2的相互作用, 从而抑制下游脂质合成通路的异常激活, 最终达到抑制肿瘤生长的效果[137]。这些研究成果共同证明, 以代谢酶的蛋白质相互作用界面为靶点, 开发变构抑制剂、蛋白降解剂及多肽药物, 是实现精准干预其非经典功能、逆转肿瘤恶性进展的有效途径。

在抑制代谢酶的非经典催化活性方面, 研究者们通过靶向代谢酶的激酶/磷酸酶活性或其他翻译后

修饰来开发选择性抑制剂。例如, 靶向HKDC1的蛋白激酶活性而非HK活性可以阻断RBBP5磷酸化进而抑制肝癌生长[97]。类似地, 槲皮素苷通过特异性抑制ALDOA在Tyr174/302/328位点的磷酸化, 有效抑制了其促癌功能[138]。丙酮酸代谢途径的二氢硫酰胺*S*-乙酰转移酶(dihydrolipoamide *S*-acetyltransferase, DLAT)被发现通过抑制支链氨基酸转氨酶2(branched chain amino acid transaminase 2, BCAT2)的活性来间接抑制亮氨酸分解代谢, 通过靶向DLAT的代谢交叉调控功能也为干预肿瘤进展提供了新思路[139]。

在干预亚细胞定位层面, 阻止从胞质、线粒体向细胞核的代谢酶异常转位已成为重要策略。研究发现, ALDOA的核转位依赖其K200位点的泛素化, 该过程可驱动*RELA*转录并促进胰腺癌进展。通过靶向ALDOA泛素化而非其酶活性, 可以有效提高p65抑制剂与化疗药物的协同抗肿瘤效果[25]。同时, 核定位的肝型磷酸果糖激酶(phosphofructokinase, liver type, PFKL) Thr562残基通过结合组蛋白脱乙酰酶抑制剂罗米地辛的锌结合基团增强其药效, 开发治疗性多肽PFKL-552-572-R8可以成功增强罗米地辛的抗肿瘤作用[140]。

在进一步拓展的干预“代谢酶-RNA相互作用”领域, 研究发现PHGDH除代谢功能外, 还可作为RNA结合蛋白通过稳定mRNA促进肝癌进展, CHENG等[141]首次发现并鉴定PHGDH的RNA结合结构域, 并通过设计RNA诱饵寡核苷酸特异性靶向PHGDH与RNA的相互作用, 联合药物协同抑制肝癌进展。研究证明, HPD可作为RBP促进肿瘤进展; 通过阻断其RNA结构域, 破坏其RNA结合功能, 能够有效抑制肿瘤发展与耐药性形成[142]。多层次干预策略的协同发展, 标志着靶向代谢酶的非经典功能的研究已从概念验证进入系统开发的新阶段。

5 总结与展望

本文系统综述了代谢酶在肿瘤进展中的非经典功能, 分别从表观遗传调控、信号转导、肿瘤微环境重塑三个方面进行了深入探讨(表2)。随着研究进展逐渐深入, 代谢酶的多功能性日益凸显: 在基因水平上, 它们通过核转位直接参与DNA转录、损伤修复、甲基化修饰及RNA稳定性维持; 在分子水平上, 通过蛋白相互作用、翻译后修饰及RNA结合等方式, 广泛调控信号通路与基因表达; 在细胞水平上, 则通过外泌体介导的细胞间通讯及代谢物分泌, 远程调控肿瘤微环境的免疫与代谢状态。

代谢酶的功能多样性与其亚细胞定位密切相关。一部分代谢酶通过核转位直接调控表观遗传与转录过程, 另一部分则通过线粒体定位影响能量代谢与信号转导[34]。而不发生定位变化的代谢酶则可通过充当RNA结合蛋白、参与蛋白互作或提供代谢物等方式发挥非经典功能。这些机制共同构成了代谢酶从代谢中心向多功能分子枢纽转变的理论基础。

随着多组学技术与基因组学、蛋白质组学、代谢组学的深度融合, 代谢酶在肿瘤中的突变、表达调控及网络互作逐渐清晰。在转化医学方面, 针对代谢酶的非经典功能的精准干预策略如变构抑制剂、蛋白降解剂、亚细胞定位阻断剂及RNA互作干扰剂, 正逐步从概念验证走向临床开发。结合免疫治疗、化疗及靶向治疗, 联合靶向代谢酶的非经典功能, 有望为克服肿瘤异质性、治疗耐药及免疫逃逸提供全新解决方案, 推动肿瘤治疗进入“代谢精准干预”新时代[143]。

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表2 代谢酶的非经典功能汇总

Table 2 Overview of the non-canonical functions of metabolic enzymes

代谢酶 Metabolic enzyme	经典代谢功能 Classical metabolic function	非经典功能 Non-canonical function	关键机制/作用 Key mechanism/action
PFKFB4	Catalyzes the synthesis and degradation of fructose-2,6-bisphosphate	Transcriptional regulation, promotes metastasis and angiogenesis	Nuclear translocation, acts as a coactivator for HIF-1α; phosphorylates and activates SRC-2/3; upregulates IL-6
SPHK1/2	Catalyzes the generation of S1P from sphingosine	Regulates immune evasion, inflammatory response	MTA3/PD-L1 axis; activates NF-κB/IL-6/STAT3 signaling axis; suppresses *IFN-β1* transcription
ALDOA	Catalyzes the degradation of fructose-1,6-bisphosphate	DNA damage repair, cell cycle regulation	Nuclear translocation, interacts with DNA-PK and ATM to enhance their kinase activity and DSB repair; stabilizes genome via ATM-PLK1 pathway
UCKL1	Catalyzes uridine/cytidine synthesis	Inhibits ferroptosis	Upregulates SLC7A11 expression
PDH/PDHE1α	Catalyzes the generation of acetyl-CoA from pyruvate	Regulates cell cycle, DNA damage repair, immune evasion	Nuclear translocation, generates acetyl-CoA for histone acetylation; modulates PPM1B/IKKβ/NF-κB pathway
LDHA	Catalyzes the generation of lactate from pyruvate	Epigenetic regulation, signal transduction, promotes invasion	Generates acetyl-CoA in the nucleus; acts as a scaffold to directly activate Rac1
ACLY	Catalyzes the generation of acetyl-CoA from citrate	Epigenetic regulation, chemotherapy resistance	Modulated by lactate, alters histone acetylation status
ACSS2	Catalyzes the generation of lactyl-CoA from lactate	Histone acetylation and lactylation, immune evasion	Acts as a lactyl-CoA synthetase, couples with KAT2A to catalyze histone lactylation
PKM2	Catalyzes the generation of pyruvate from phosphoenolpyruvate	Transcriptional regulation, angiogenesis, intercellular communication, translation regulation	Nuclear translocation, acts as a protein kinase to phosphorylate histone H3/β-catenin; acts as an RNA-binding protein to inhibit translation; taken up by stromal cells via exosomes
PGAM1	Catalyzes the interconversion of 3-phosphoglycerate and 2-phosphoglycerate	Promotes metastasis, angiogenesis, drug resistance	Interacts with ACTA2/ACTG1; transmitted via exosomes; disrupting its interaction with JAK2/STAT3 reverses drug resistance
GAPDH	Catalyzes the generation of D-glycerate 1,3-bisphosphate from glyceraldehyde 3-phosphate	Senses oxidative stress, post-transcriptional regulation	Senses H_2O_2 signal and transduces it to MAPK pathway; binds to *IFN-γ*, *CSF-1* mRNAs to regulate their stability or translation
PHGDH	Catalyzes the generation of 3-phosphohydroxypyruvate from 3-phosphoglycerate	Regulates ferroptosis, mitochondrial respiration, transcriptional regulation, metabolic plasticity	Binds PCBP2 to stabilize *SLC7A11* mRNA; activates *MYC* transcription in the nucleus; interacts with ANT2 to promote mitochondrial translation; acts as an RBP to stabilize mRNA
ENO1	Catalyzes the reversible conversion between 2-phosphoglycerate and phosphoenolpyruvate	Post-transcriptional regulation	Acts as an RNA-binding protein, degrades *IRP1* mRNA, promotes translation of *YAP1* and other mRNAs
HK2	Catalyzes the generation of glucose-6-phosphate from glucose	Immune evasion	Detaches from mitochondria, degrades IκBα to activate NF-κB pathway, upregulates PD-L1
CD73 (NT5E)	Catalyzes the generation of adenosine from AMP	Transcriptional regulation, establishes immunosuppressive microenvironment	Tanscriptional upregulation of *CCL5* via ADORA2A-p38-STAT1 pathway to recruit Tregs

S1P: 鞘氨醇-1-磷酸; HIF-1α: 缺氧诱导因子1α; DSB: DNA双链断裂; acetyl-CoA: 乙酰辅酶A; lactyl-CoA: 乳酰辅酶A; RBP: RNA结合蛋白; Tregs: 调节性T细胞。

S1P: sphingosine-1-phosphate; HIF-1α: hypoxia inducible factor 1 alpha; DSB: double-strand break; acetyl-CoA: acetyl coenzyme A; lactyl-CoA: lactyl coenzyme A; RBP: RNA-binding protein; Tregs: regulatory T cells.

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