·综 述·

乳腺癌中能量代谢重编程的致癌作用和机制

The carcinogenic roles and mechanisms of energy metabolism reprogramming in breast cancer

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[摘　要]　乳腺癌（BC）是全球最常见的恶性肿瘤之一，其细胞代谢具有高度的可塑性，可以根据环境变化适应不同的代谢需求，这种现象被称为代谢重编程。BC细胞通过调控多种代谢通路，包括糖代谢、脂质代谢、谷氨酰胺代谢等，改变细胞表型，促进细胞增殖、侵袭、转移及耐药性。糖代谢的关键蛋白GLUT1、HK2、PHGDH等的表达紊乱促进了糖酵解过程，增强肿瘤细胞的生长与转移能力。脂肪酸合成和氧化代谢的平衡为BC细胞提供了生存和增殖的优势。谷氨酰胺作为细胞的重要碳源和氮源，一方面通过补充作用增强三羧酸循环的通量，进一步支持BC细胞的代谢需求，另一方面通过维持氧化还原平衡促进BC细胞的免疫逃避及治疗耐药。本文旨在全面总结BC中能量物质代谢的重编程现象及其已知的关键调控机制，为发现新的治疗靶点、优化治疗策略、阐明耐药机制以及克服耐药性提供宝贵参考。

[关键词]　乳腺癌；代谢重编程；葡萄糖代谢；脂质代谢；谷氨酰胺代谢

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乳腺癌（breast cancer, BC）是全球最常见的恶性肿瘤之一。BC细胞等多种肿瘤细胞的代谢具有高度可塑性，在应对不良刺激时，能适应性地调整对特定代谢物的利用途径、水平和种类[1]。肿瘤细胞通过调控代谢物驱动基因的表达、细胞表型及肿瘤微环境，促进自身的增殖、侵袭、转移以及对治疗的耐受，这一现象被称为代谢重编程[2-4]。BC细胞在多种能量物质代谢途径中的重编程现象、调控机制、生物学作用已逐步被揭示，主要涉及葡萄糖代谢、脂质代谢和氨基酸代谢。本文旨在探讨这些代谢重编程事件对BC细胞表型的影响，归纳总结背后的驱动分子和机制，为进一步研究代谢重编程关键步骤和潜在靶点提供参考。

1　糖代谢重编程促进BC细胞增殖、转移、干性及耐药性

在BC细胞的糖代谢通路中，关键蛋白的表达或活性紊乱是代谢重编程的重要驱动因素。为了适应高能量需求或应对治疗压力，BC细胞在c-MYC、KRAS等肿瘤驱动因子的作用下，激活关键蛋白的转录或通过构象调节增强其稳定性，从而促进糖酵解或其后续反应。另外，在此过程中产生的代谢产物还会为其他代谢途径使用，包括己糖胺途径、磷酸戊糖途径和丝氨酸生物合成途径等[5]。这种高效的能量供应和物质利用有助于BC细胞的快速增殖、远处转移、上皮间质转化及化疗抵抗等，为BC治疗提供了潜在的新靶点。本文深入地对BC糖代谢重编程

中关键分子，包括葡萄糖转运体（glucose transporter, GLUT）、己糖激酶2（hexokinase 2, HK2）、磷酸甘油酸脱氢酶（phosphoglycerate dehydrogenase, PHGDH）和丙酮酸激酶M2（pyruvate kinase M2, PK M2）等，在乳腺癌中的作用及其调控机制（如图1所示）进行综述。脂质代谢重编程与谷氨酰胺代谢重编程行文安排类似。

1.1　GLUT表达上调通过提高葡萄糖转运效率促进BC细胞增殖和耐药性

GLUT由SLC2基因编码，负责葡萄糖摄取。人类基因组编码14种GLUT亚型，它们具有不同的底物结合偏好[6]。GLUT1作为主要膜性转运体，广泛高表达于三阴性乳腺癌（triple negative breast cancer, TNBC）以及管腔A型、管腔B型和人表皮生长因子受体2阳性型（human epidermal growth factor receptor 2, HER2）（HER2+）等BC亚型中[7-9]。GLUT1表达上调与细胞糖代谢增强和增殖促进密切相关[10-11]。靶向抑制GLUT1已成为治疗糖酵解依赖性BC的重要策略。例如，BAY-876通过抑制GLUT1在TNBC中的功能，干扰糖酵解和氧化磷酸化（oxidative phosphorylation, OXPHOS）过程，从而抑制

肿瘤增殖[12]。此外,二甲双胍与BAY-876联用,通过同步干预OXPHOS和糖酵解,促进肿瘤能量剥夺并抑制其生长[13]。GLUT1抑制剂WZB117通过阻断BC细胞葡萄糖摄取,能协同恢复阿霉素耐药的MCF-7细胞对阿霉素的敏感性[14]。在雌激素受体(estrogen receptor, ER)阴性ER⁻的BC中,Src激活可上调GLUT1表达促进葡萄糖摄取,而Src抑制剂saracatinib可下调GLUT1活性,抑制肿瘤增殖[15]。MYC作为经典原癌基因,其编码的c-MYC转录因子

在BC中高表达,可以调控GLUT1和A型乳酸脱氢酶(lactate dehydrogenase A, LDHA)并促进糖酵解[16]。CLDN6在BC组织中表达较低,其过表达可减少c-MYC转录从而抑制糖酵解;相反,桦木酸(BA)激活Caveolin-1后可抑制c-MYC,减少BC细胞糖酵解[17]。总之,GLUT1的表达和活性受多种因素调控,这些因素共同构成复杂的调控网络,为BC中糖代谢通路的联合治疗提供了潜能。
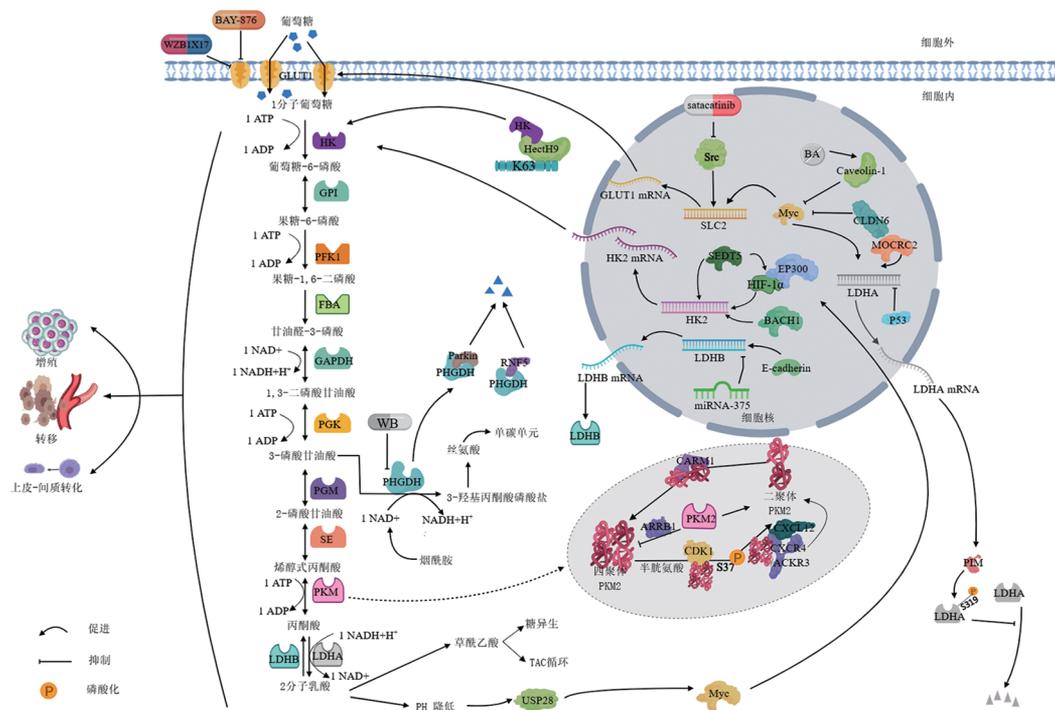

图1　BC糖代谢重编程调控机制示意图

1.2 HK2表达或活性上调激活糖酵解并促进BC细胞干性、转移和增殖

己糖激酶(hexokinase, HK)是糖酵解过程的限速酶,人体中HK有HK1和HK2两种同工酶。泛癌数据显示,HK2在BC、肺腺癌、宫颈癌等多种癌症中高表达,并促进肿瘤细胞干性、转移和增殖[18]。HK2可通过非酶作用上调上皮-间质转化(epithelial-mesenchymal transition, EMT)相关转录因子SNAIL的蛋白水平,进而促进BC细胞转移[19]。缺氧诱导因子1α(Hypoxic inducible factor 1α,HIF-1α)、组蛋白赖氨酸甲基转移酶SETD5、转录因子BACH1等均能增强HK2转录,促进糖酵解及肿瘤细胞增殖[20-22]。在BC体外模型中,聚达丁(PD)与2-脱氧-D-葡萄糖(2-DG)的联合治疗可降低HK2表达、抑制糖酵解表型,展示潜在抗癌效果[23]。此外,HK2抑制剂BNBZ通过抑制糖酵解也表现出良好的抗癌活性[24]。E3连接酶HectH9通过K63连锁泛素化作用激活HK2,抑

制HectH9/HK2通路可减少活性氧(reactive oxygen species, ROS)介导的癌症干细胞样细胞扩增[25]。

1.3 PHGDH催化糖酵解与丝氨酸合成促进BC细胞生长、增殖、转移及干性

在糖酵解过程中,PHGDH催化3-磷酸甘油酸生成3-磷酸羟基丙酮酸。PHGDH与BC细胞的生长、转移、增殖密切相关[26]。PHGDH是丝氨酸合成途径中的限速酶,而丝氨酸是嘌呤和脱氧核糖核苷合成的必需单碳源。在肿瘤干细胞的体外诱导模型中,PHGDH表达与干性因子(如Oct4)的mRNA水平呈正相关,抑制PHGDH可诱导雷帕霉素(p-mTOR)非依赖性自噬并促进多向分化[27]。睡茄内酯类成分(WA)与PHGDH结合后可使其失活,导致谷胱甘肽(glutathione, GSH)合成减少、细胞内ROS升高,最终抑制肿瘤增殖[28]。PHGDH的功能依赖于氧化还原辅因子(NAD⁺),而BC细胞中NAD⁺主要来源于烟酰胺补救途径[29]。NAD⁺耗尽后,PHGDH依赖的丝氨酸合

成减少。泛素连接酶Parkin和RNF5可与PHGDH相互作用并促使其降解,从而间接抑制丝氨酸合成[30]。综上,PHGDH抑制剂是一种极有潜力的肿瘤增殖抑制药物,针对PHGDH或其介导的丝氨酸合成通路的靶向药物研发具有巨大潜力。

1.4 PKM2二聚体介导丙酮酸向乳酸转化促进BC细胞生长、增殖、耐药性及存活

丙酮酸激酶(pyruvate kinase, PK)将磷酸烯醇式丙酮酸(phosphoenolpyruvic acid, PEP)转化为丙酮酸并产生ATP。在BC细胞中,丙酮酸羧化酶将丙酮酸转化为草酰乙酸,用于糖异生和补充三羧酸循环(tricarboxylic acid cycle, TAC)[31]。在多种PK同工酶中,PKM2在肿瘤中的表达更具优势。PKM2有四聚体和二聚体两种形式,四聚体对PEP亲和力高,二聚体则较低[32]。肿瘤细胞中,二聚体形式的PKM2是调节糖酵解的限速步骤,使葡萄糖代谢从正常呼吸链转向乳酸产生,促进肿瘤细胞生长增殖[33]。在他莫昔芬耐药的ER+ BC细胞中,PKM2抑制剂与他莫昔芬联用可逆转他莫昔芬耐药[34]。PKM2转录上调能促进BC发生发展。例如,YTHDF1能识别并修饰PKM2 mRNA的m6A,增加其表达,促进BC的发生和转移[35]。此外,分子构象变化对PKM的活性调控也起着重要作用。共激活因子相关精氨酸甲基转移酶1通过精氨酸甲基化PKM2,促进四聚体的形成[36];半胱氨酸可将野生型四聚体PKM2转变为二聚体[37]。细胞周期依赖性激酶CDK1磷酸化PKM2的S37位点,促进二聚体形成,从而支持肿瘤代谢重编程并抑制细胞死亡[38]。此外,β-抑制蛋白1与PKM2结合,抑制其四聚化[39]。趋化因子CXCL12与CXCR4和ACKR3结合后可诱导ARRBP2与PKM2解离,促使PKM2四聚体转变为二聚体[40]。

1.5 LDH亚型适应性转换调控糖酵解促进BC细胞转移、增殖或存活

LDH在糖酵解中主要将丙酮酸还原成乳酸,而乳酸介导的局部酸性微环境有助于肿瘤细胞的迁移和免疫抑制[41]。LDH包括LDHA、LDHB和LDHC。低氧时,LDHA倾向将丙酮酸还原为乳酸,而LDHB则催化丙酮酸和乳酸相互转化,促进TNBC增殖[42]。敲低LDHA或LDHB可减少乳酸生成,抑制BC细胞迁移,二者或为潜在靶点[43]。LDHC通过维持细胞形态促进BC发展,沉默LDHC可诱导细胞凋亡[44]。LDHA的表达与活性受转录和蛋白质水平调控。芳香化酶抑制剂(AI)耐药的乳腺肿瘤中,长链非编码RNA(lncRNA)DIO3OS上调可促进LDHA转录,联合靶向DIO3OS与AI治疗可增强对ER+ BC的疗效[45]。微氏菌CW型锌指2(microchidia family CW-

type zinc finger 2, MORC2)受c-MYC的调控,增强LDHA的转录活性,促进BC转移[46]。另外,丝氨酸-苏氨酸家族成员PIM激酶磷酸化LDHA-S319位点,可提高LDHA的稳定性和活性[47]。而抑癌基因P53编码的转录因子能与LDHA的启动子结合,抑制LDHA的转录[48]。此外,E-钙黏蛋白(E-cadherin)促进LDHB的转录[49]。miRNA-375过表达可下调BC细胞中LDHB的转录水平,并增强有氧糖酵解和乳酸生成[50]。

2 脂质代谢重编程促进BC细胞存活、增殖、转移及耐药性

脂肪酸(fatty acid, FA)代谢重编程在BC细胞中扮演着重要角色,主要参与生物合成和能量供应。BC细胞通常会高表达脂肪酸转运蛋白,如CD36和FABP家族成员,从而增强其摄取外界FA的能力,获取丰富的脂质,以满足自身快速增殖和生长的能量需求。此外,关键酶ACC和FASN在AMPK的能量感应调控下能够合理调节BC细胞内的FA合成途径,从而帮助细胞抵抗铁死亡、维持氧化还原平衡、增殖、侵袭和迁移等[51]。肿瘤细胞还会根据自身所处的微环境变化调节脂肪酸氧化活性,从而在葡萄糖缺乏等应激条件下为细胞提供维持生存和增殖所必须的能量及抗氧化物质。总之,脂质代谢重编程为BC细胞提供了生存和增殖的优势,深入理解其机制有助于开发新的治疗策略。BC脂质代谢重编程调控机制如图2所示。

2.1 脂质摄取相关蛋白促进BC细胞侵袭、转移及耐药性

FA不仅是细胞膜的主要成分,还参与细胞信号传递等重要功能。BC获取FA包括从头合成以及外源性摄取两条途径。CD36和FA结合蛋白(fatty acid binding proteins, FABP)等转运蛋白是BC摄取外源性FA的主要蛋白分子[52]。CD36常在抗癌药物压力下表达上调,促进外源性FA摄取和耐药[53],还能激活信号转导和转录激活因子3(signal transducer and activator of transcription 3, STAT3)等相关信号通路,促进迁移、侵袭[54]。TNBC细胞在TKI治疗过程中上调FABP4,增强适应性并抵抗铁死亡[55]。核受体Nur77可以抑制CD36和FABP4的转录,阻断脂质摄取并抑制肿瘤生长。然而,过氧化物酶增殖物激活受体γ(peroxisome proliferator-activated receptor γ, PPAR-γ)能够降解Nur77,从而阻断其抑癌作用[56-57]。值得注意的是,细胞视黄酸结合蛋白2(cellular retinoic acid binding protein 2, CRABP2)也属于FABP家族,在ER+ BC中激活Hippo通路,抑制侵袭和转

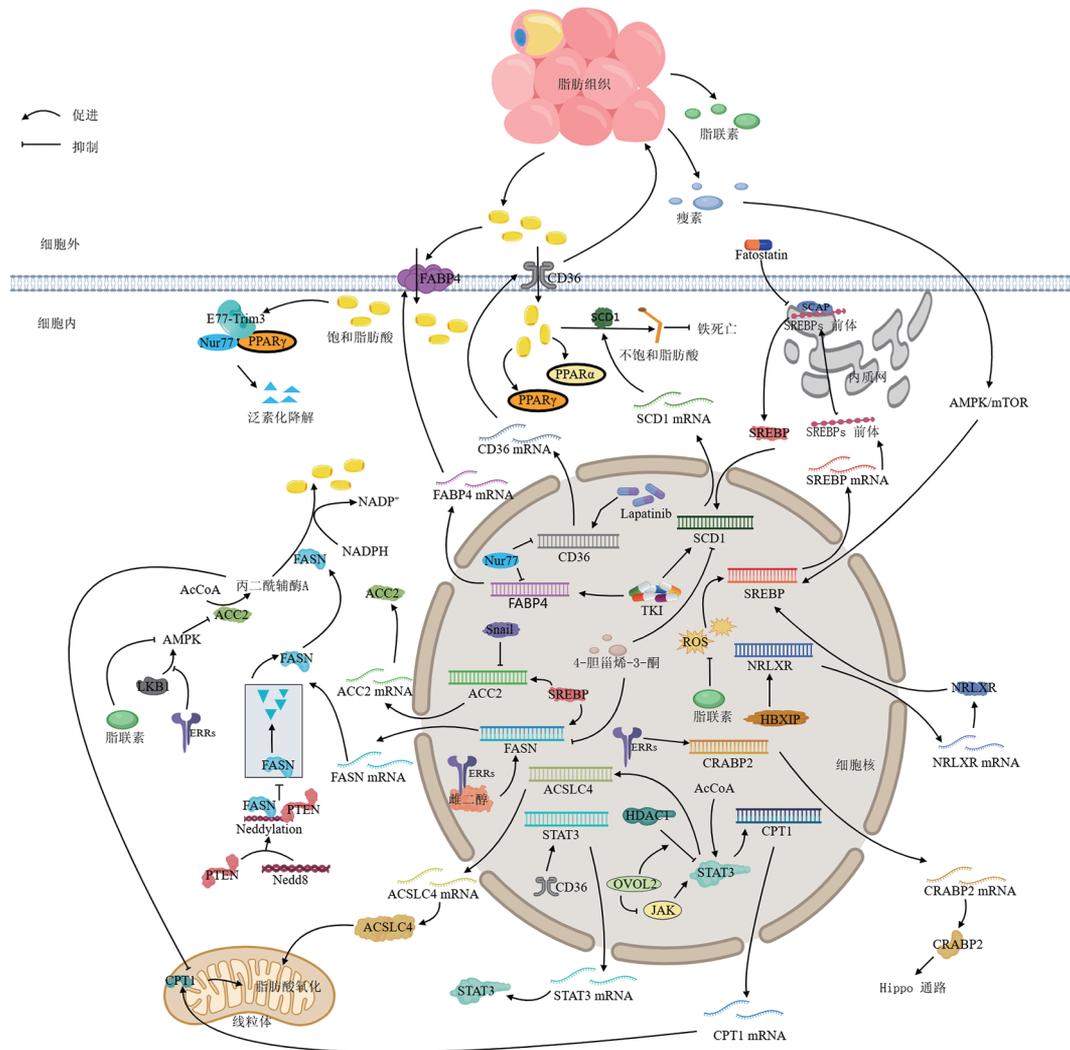移；而在 ER⁻ BC 中则促进侵袭和转移[58]。综上，BC 肿瘤细胞中外源性 FA 的摄取增加时有发生，靶向调控相关分子或通路具有潜在的抗癌作用。

图2　BC 脂质代谢重编程调控机制示意图

2.2　ACC2 表达或活性根据能量状态适应性变化促进 BC 细胞的生长和存活

　　FA 合成为 BC 细胞提供能量，有助于细胞膜结构的构建与信号转导。在 KRAS 激活的癌症中，外源性油酸诱导磷脂酸合成，激活 mTORC2/AKT/ATP-柠檬酸裂解酶（ATP-citrate lyase, ACLY）信号通路，促使柠檬酸转化为乙酰辅酶 A（AcCoA）和草酰乙酸，为 FA 和核苷酸合成提供原料[59]。在 BC 细胞中，FA 合成受到细胞内能量状态的调控。乙酰辅酶 A 羧化酶 2（acetyl-CoA carboxylase 2, ACC2）与脂肪酸合成酶（fatty acid synthase, FASN）等是 FA 合成的关键酶。葡萄糖缺乏时，磷酸腺苷激活的蛋白激酶（AMP-activated protein kinase, AMPK）激活能够抑制 ACC2 的活性，减少 ATP 消耗，帮助肿瘤细胞生存[60]。类似地，Snail 通过直接抑制 ACC2 的表达，降低细胞内的脂肪酸合成并增强脂肪酸氧化（fatty acid oxidation,

FAO），有助于 BC 细胞获取能量并适应缺氧环境[61]。在 ER⁺ BC 中，能量应激时，脂联素通过激活 AMPK 抑制脂质合成；而非能量应激状态下，ERα 激活则降低 AMPK 活性，促进脂质合成和肿瘤发展[62]。4-胆甾烯-3-酮是一种胆固醇氧化衍生物，能够下调 ER⁻ BC 细胞中 ACC1、FASN 和硬脂酰辅酶 A 脱饱和酶 1（stearoyl-CoA desaturase 1, SCD1）等脂质代谢相关酶。

2.3　FASN 表达或稳定性增强促进 BC 细胞的增殖、转移、耐药性以及氧化还原平衡

　　FASN 能够催化 ACC2 的产物丙二酰 CoA 与 AcCoA 生成棕榈酸。在 BC 细胞中，即便外源性 FA 充足，FASN 介导的 FA 合成仍异常增强，提示肿瘤对该信号传导的固有依赖[63]。FASN 能够促进体外组织的血管萌芽，敲低内皮细胞中的 FASN，会导致丙二酰 CoA 积累，从而抑制 mTOR 活性，阻止内皮细胞的

增殖与迁移,进而抑制新血管的形成[64]。在HER2^{+}小鼠BC的脑转移模型中,ACC2与FASN等酶的表达均上调,提示脂质合成在肿瘤转移中扮演重要角色[65]。此外,FASN合成FA时消耗大量NADPH,有助于维持肿瘤细胞的氧化还原平衡;FASN抑制可导致NADPH积累,诱发氧化还原失调,激活促凋亡激酶JNK和P38MAPK,为肿瘤治疗提供了一个潜在的靶点[66]。在ER(+)BC细胞中,雌二醇以ERα依赖的方式刺激FASN表达并促进FA合成,导致他莫昔芬耐药[67]。此外,抑癌因子PTEN与Nedd8缀合形成的复合物能与FASN蛋白结合并促进其稳定性,从而促进肿瘤增殖[68]。

2.4　SREBP通过上调FA代谢途径关键酶促进BC细胞的生长和存活

甾醇调节元件结合蛋白(sterol regulatory element-binding protein, SREBP)激活能够上调ACC2、FASN、ACLY、SCD1等多种脂质代谢相关酶的表达,在BC的脂质代谢重编程过程中发挥重要作用。SREBP裂解激活蛋白(SREBP cleavage activator protein, SCAP)是SREBP的运输和激活核心蛋白,只有在SCAP的作用下,SREBP前体才能在内质网内被加工和激活[69]。Fatostatin作为SREBP抑制剂,通过结合SCAP阻断其激活作用,展现出抑肿瘤的潜力[70]。SREBP的表达及活性受到多方面的调控。脂肪组织分泌的瘦素和脂联素在SREBP表达调控中发挥相反作用。在ER[+]BC细胞中,瘦素能够激活AMPK和mTOR信号通路上调SREBP-1的表达并增强其活性,从而促进FA合成基因的转录和细胞生长[71]。与之相对,脂联素能够降低ROS水平,间接抑制SREBP的过度激活,保护细胞免受脂质积聚的损害[50]。此外,癌蛋白HBXIP能够激活NRLXR核受体上调SREBP-1c的表达,促进FA合成与BC细胞生长[72]。肿瘤中PI3K/AKT/mTOR信号通路的异常激活可以上调SREBP1的表达,通过SCD1促进饱和FA向单不饱和FA转化,帮助BC细胞抵抗脂质过氧化引发的铁死亡[73]。总之,SREBP在BC脂质代谢中具有重要调控作用,其机制研究有望推动精准靶向治疗。

2.5　FA氧化增强促进BC细胞增殖、转移及耐药性

FAO是细胞重要的产能途径,可以将FA分解为AcCoA并生成大量ATP。FAO的限速酶肉毒碱棕榈酰转移酶1A(carnitine palmitoyltransferase 1A, CPT1A)及其调控因子STAT3在这一过程中发挥关键作用。FAO活性上调的BC细胞间质特征更明显,如形态改变(例如增强的迁移性)和细胞间黏附能力下降等,抑制FAO可减缓或阻止肿瘤转移[74]。高表达的CDCP1通过促进FAO,减少脂滴,增强TNBC细胞的能量获取、增殖和迁移能力[15]。FAO产物AcCoA作为乙酰化底物,促进STAT3乙酰化,从而上调ACSLC4,增强线粒体活性,帮助TNBC细胞抵抗紫杉醇诱导的凋亡[75]。而Ovo样蛋白OVOL2则可通过抑制JAK转录、降低STAT3磷酸化,减少CPT1A和CPT1B的转录,抑制TNBC细胞的能量生成和抗氧化能力[76]。FAO的增强在其他类型的BC细胞中也至关重要,异常激活的JAK/STAT3可促进CPT1B表达,支持乳腺癌干细胞(breast cancer stem cell, BCSC)增殖和存活[77]。FAO的激活也与他莫昔芬耐药的ER[+]BC耐药性相关[78]。

3　谷氨酰胺代谢促进BC细胞能量供应、抗氧化防御与细胞转移

BC细胞快速增殖依赖于氨基酸代谢提供的大量碳源和氮源,其中谷氨酰胺的代谢起着关键桥梁作用,也是乳腺癌中氨基酸代谢重编程研究的关键对象。与正常细胞相比,BC细胞常表现出对谷氨酰胺的依赖性。在缺氧等恶劣的肿瘤微环境中,糖酵解产生的能量可能不足以满足癌细胞的需求,谷氨酰胺代谢的能量补充尤为重要。谷氨酰胺代谢过程中产生的还原型辅酶,如NADPH,充当抗氧化剂,参与GSH的再生过程和ROS清除,保护肿瘤细胞免受氧化应激损伤,促进了肿瘤的恶性转化、耐药性发展及免疫逃避。此外,BC细胞通过对谷氨酰胺的吸收和转化,促进了ATP等能量物质的产生,并为核苷酸和脂质合成提供了碳骨架。BC谷氨酰胺代谢重编程调控机制如图3所示。

3.1　谷氨酰胺代谢通过优化物质供给与能量产生促进BC细胞生长和转移

尽管谷氨酰胺是非必须氨基酸,但大多数恶性细胞在缺乏谷氨酰胺时难以存活与增殖。BC细胞通过利用谷氨酰胺获取碳源和氮源,支持核苷酸、葡萄糖胺、FA和其他非必需氨基酸的合成[79-81]。谷氨酰胺通过转运体ASCT2或SLC1A5进入细胞后分解,激活mTORC1通路,促进蛋白质合成和细胞生长。抑制谷氨酰胺相关转运蛋白可显著抑制BC细胞的增殖并诱导凋亡[82]。在KRAS驱动的肿瘤中,同时抑制ACLY和谷氨酰胺代谢,细胞可因代谢紊乱和能量危机而死亡[59]。谷氨酰胺在谷氨酰胺酶的作用下水解为谷氨酸,后者参与了其它氨基酸的合成。谷氨酸代谢生成α-酮戊二酸(α-ketoglutarate, α-KG),可提高TAC通量,促进长链FA合成和TNBC细胞的生长[83]。此外,在缺氧条件下,BC细胞中谷氨酰胺来源的AcCoA生成增加有助于脂质合成。Cullin-RING连

接酶（cullin-RING ligase, CRL）与斑点型 POZ 蛋白形成的复合物能够通过泛素化降解 ASCT2，抑制谷氨酰胺摄取与肿瘤生长。而 Neddylation 对 CRL 的类泛素化作用可解除这种抑制[84]。谷氨酰胺通过增强 BC 细胞的代谢活性，增强 ATP 合成和释放以及微管的稳定性和刚性，有助于细胞收缩和运动、转移和侵袭[85]。SLC38A3 是一种重要的谷氨酰胺转运体，能够抑制 GSK-3β，间接促进 β-连环蛋白（β-catenin）及其它 EMT 相关分子的表达，调控谷氨酰胺代谢相关基因，支持 BC 细胞的转移[86]。
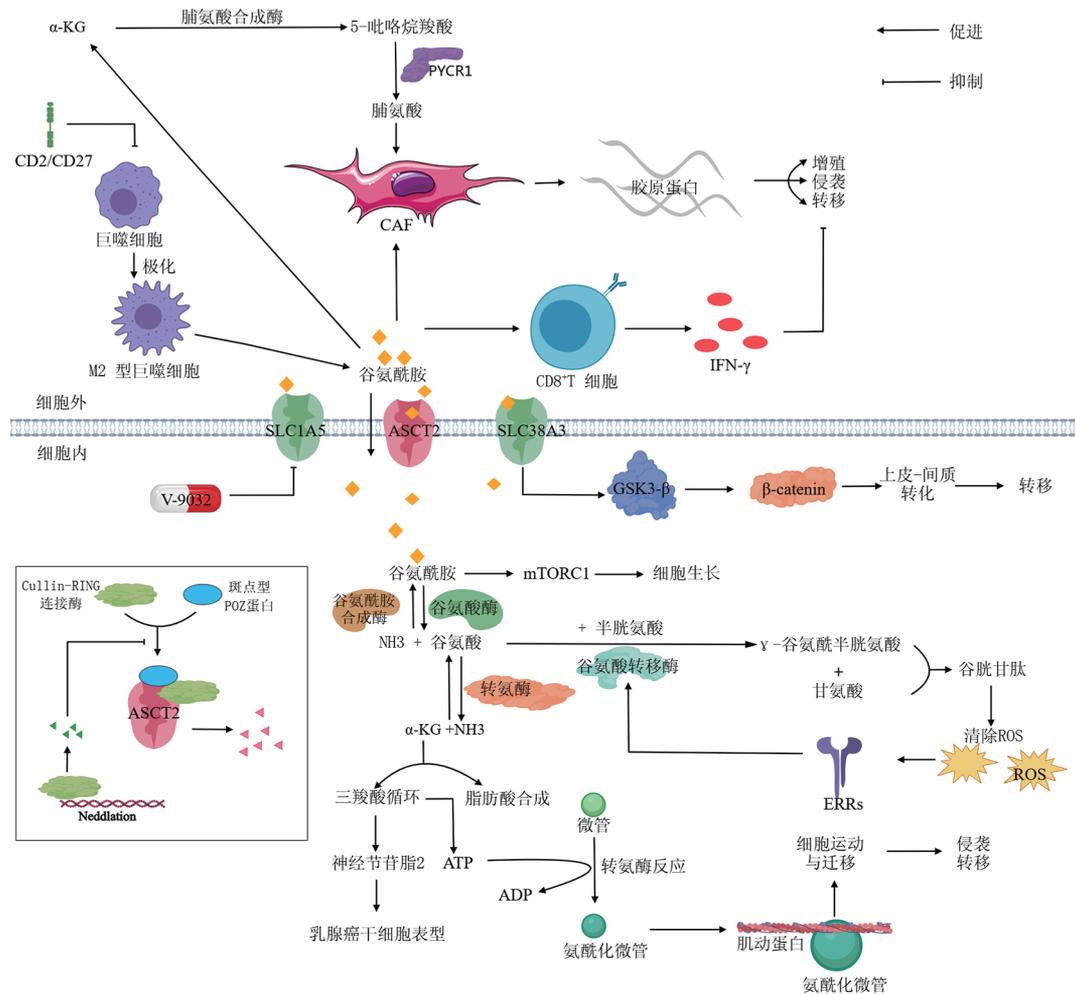

图3　BC谷氨酰胺代谢重编程调控机制示意图

谷氨酰胺代谢也能通过肿瘤微环境间接影响 BC 细胞侵袭、转移或增殖。首先，高浓度的谷氨酰胺能诱导癌症相关成纤维细胞（cancer-associated fibroblast, CAF）迁移，进而促进上皮肿瘤细胞的侵袭[87]。谷氨酰胺来源的 α-KG 生成 5-吡咯烷羧酸，再由脯氨酸还原酶 1（pyrroline-5-carboxylate reductase 1, PYCR1）还原为脯氨酸，有助于胶原蛋白的生成。在 TNBC 中靶向 PYCR1 显著抑制 BC 细胞的生长和转移[88]。其次，浸润性 T 细胞正常激活并发挥免疫效应具有一定的谷氨酰胺依赖性。敲低 TNBC 肿瘤细胞中的谷氨酸脱氨酶（glutaminase, GLS）可增加 CD8⁺ T 细胞的谷氨酰胺可用性，促进其 γ 干扰素等免疫活性物质的分泌，从而发挥抗肿瘤作用[89]。使用谷氨酰胺代谢抑制剂 V-9302 选择性抑制 TNBC 肿瘤细胞对谷氨酰胺的摄取和代谢，能够间接满足肿瘤组织中淋巴细胞对谷氨酰胺的需求[90]。最后，过表达 TNBC 细胞中的免疫共刺激分子 CD2/CD27 能够抑制肿瘤微环境中 M2 型巨噬细胞的极化，减少 M2 型巨噬细胞对 BC 细胞的氨基酸代谢支持，进而抑制 BC 细胞的脑转移[91]。BC 细胞与免疫细胞之间的谷氨酰胺竞争为局部靶向抑制 BC 细胞谷氨酰胺的摄取和利用、同时增强免疫细胞功能提供了新的治疗思路。

3.2　谷氨酰胺代谢促进氧化还原平衡介导 BC 细胞耐药及免疫逃逸

谷氨酰胺为 BC 细胞提供了 GSH 合成的底物，帮助其抵抗氧化应激。SLC38A5 是关键的谷氨酰胺转运蛋白，在多种 BC 细胞系中高表达并促进顺铂等化

疗药物的耐药性[92]。缺乏细胞外谷氨酰胺或抑制SLC38A5会限制GSH合成,增加ROS,引发氧化损伤[93]。在葡萄糖和乳酸耗竭时,谷氨酰胺回补线粒体内TCA过程可提高NADH/NAD$^+$比值,维持氧化还原稳态[94]。在TNBC中,神经节苷脂2(ganglioside GM2, GD2)是BCSC的标志物,GD2表达越高,CD44$^+$/CD24$^-$ BCSC比例越大。谷氨酰胺通过促进TCA循环和脂质合成,诱导GD2$^+$BCSC表型,尤其是在代谢应激下。SLC1A5抑制剂V-9302能显著减少BCSC特性,抑制mTOR通路,并与紫杉醇协同作用,诱导TNBC细胞凋亡[95]。另外,肝脏X受体激动剂1E5通过下调谷氨酰胺代谢相关基因的转录,减少细胞内GSH水平,增加ROS,从而抑制TNBC细胞增殖[96]。雌激素相关受体(ERR)作为ROS传感器,可调节谷氨酰胺代谢,帮助BC细胞维持氧化还原平衡或适应氧化应激[97]。此外,肿瘤微环境中的CD8$^+$T细胞通过上调SLC6A14来满足谷氨酰胺需求,促进GSH合成,改善氧化还原平衡,从而维持抗TNBC的免疫功能[90]。

4　结　论

代谢重编程在BC中普遍发生,其中最常见的3种类型为葡萄糖有氧糖酵解、FA代谢紊乱和谷氨酰胺依赖。相关信号通路和调节因子通过调控糖酵解途径中的关键酶(如GLUT、HK、PHGDH、PK、LDH)表达及活性,影响代谢过程。糖酵解、磷酸戊糖途径以及乳酸、AcCoA、NADPH等代谢产物为FA和胆固醇合成提供底物。FA的合成与分解受细胞能量状态调节,AMPK等通路参与其中。FASN、ACC等关键酶的活性与稳定性是FA合成的控制点;同时,FABP家族调节的外源性FA摄取,影响BC的生长、转移与侵袭,并与HER和/或激素受体的表达水平密切相关。此外,SREPB、瘦素、脂联素等因子在FA代谢中发挥重要作用。谷氨酰胺作为碳源和氮源,促进核苷酸和脂质合成,特别是在TNBC中,谷氨酰胺的依赖性更为显著。BC细胞与肿瘤相关效应性T细胞等免疫细胞之间的谷氨酰胺竞争为抗肿瘤免疫治疗提供了新思路。谷氨酰胺代谢通过促进胶原蛋白合成影响微管强度,增强BC的转移与侵袭能力。值得注意的是,除了本文关注的三大能量代谢物质,非供能物质在BC发生与发展中也起着重要作用。例如,维生素D和C具有抗肿瘤作用[98],而维生素B3家族的烟酰胺核糖则可促进TNBC的脑转移[99]。微量元素如氯化钴(CoCl2)能模拟缺氧,诱导HIF-1α蛋白积累,改变缺氧相关基因的表达,从而影响血管生成和细胞凋亡[100]。总之,乳腺癌代谢重编程的相关研究

不仅揭示了潜在的机制,还为发现新的治疗靶点提供了新思路,为临床靶向治疗及联合用药方案提供了更多可能。

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所有作者声明无任何利益冲突。

[参 考 文 献]

[1] ARNER E N, RATHMELL J C. Metabolic programming and immune suppression in the tumor microenvironment[J]. Cancer Cell, 2023, 41(3): 421-433. DOI:10.1016/j.ccell.2023.01.009.

[2] CHEN L H, HUANG L X, GU Y, et al. Lactate-lactylation hands between metabolic reprogramming and immunosuppression[J/OL]. Int J Mol Sci, 2022, 23(19): 11943[2025-07-15]. https://pubmed. ncbi.nlm.nih.gov/36233246/. DOI:10.3390/ijms231911943.

[3] ZUO Q Y, KANG Y B. Metabolic reprogramming and adaption in breast cancer progression and metastasis[J]. Adv Exp Med Biol, 2025, 1464: 347-370. DOI:10.1007/978-3-031-70875-6_17.

[4] WANG X Y, YANG X X, SHANG P F, et al. Metabolic reprogramming of glutamine involved in tumorigenesis, multidrug resistance and tumor immunity[J/OL]. Eur J Pharmacol, 2023, 940: 175323[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/36535492/. DOI:10.1016/j.ejphar.2022.175323.

[5] WU X J, TAN X N, BAO Y Q, et al. Landscape of metabolic alterations and treatment strategies in breast cancer[J/OL]. Genes Dis, 2025, 12(5): 101521[2025-07-15]. https://pubmed.ncbi.nlm.nih. gov/40548063/. DOI:10.1016/j.gendis.2025.101521.

[6] ISMAIL A, TANASOVA M. Importance of GLUT transporters in disease diagnosis and treatment[J/OL]. Int J Mol Sci, 2022, 23(15): 8698[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/35955833/. DOI:10.3390/ijms23158698.

[7] ZHU P, LIU G P, WANG X, et al. Transcription factor c-Jun modulates GLUT1 in glycolysis and breast cancer metastasis[J/OL]. BMC Cancer, 2022, 22(1): 1283[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/ 36476606/. DOI:10.1186/s12885-022-10393-x.

[8] OKCU O, SEN B, OZTURK C, et al. GLUT-1 expression in breast cancer[J]. Turk Patoloji Derg, 2022, 38(2): 114-121. DOI:10.5146/ tjpath.2021.01557.

[9] HANBAZAZH M, SAMMAN A, SAMARGANDY S, et al. Prognostic value of glucose transporter proteins-1 (GLUT1) in breast carcinoma[J/OL]. Libyan J Med, 2023, 18(1): 2283953 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/37988377/. DOI: 10.1080/19932820.2023.2283953.

[10] NILCHIAN A, GIOTOPOULOU N, SUN W W, et al. Different regulation of Glut1 expression and glucose uptake during the induction and chronic stages of TGFβ1-induced EMT in breast cancer cells[J/OL]. Biomolecules, 2020, 10(12): 1621[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/33271824/. DOI: 10.3390/ biom10121621.

[11] SHI Y Z, KOTCHETKOV I S, DOBRIN A, et al. GLUT1 overexpression enhances CAR T cell metabolic fitness and anti-tumor efficacy[J]. Mol Ther, 2024, 32(7): 2393-2405. DOI:10.1016/ j.ymthe.2024.05.006.

[12] SCHUMACHER T J, IYER A V, RUMBLEY J, et al. Exploring the

impact of mitochondrial-targeting anthelmintic agents with GLUT1 inhibitor BAY-876 on breast cancer cell metabolism[J/OL]. BMC Cancer, 2024, 24(1): 1415[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/39550554/. DOI:10.1186/s12885-024-13186-6.

[13] WEI X J, HAN R L, GAO Y, et al. Boosting energy deprivation by synchronous interventions of glycolysis and oxidative phosphorylation for bioenergetic therapy synergetic with chemodynamic/photothermal therapy[J/OL]. Adv Sci, 2024, 11(23): e2401738[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/38489668/. DOI:10.1002/advs.202401738.

[14] DE A, WADHWANI A, SAURAJ, et al. WZB117 decorated metformin-carboxymethyl chitosan nanoparticles for targeting breast cancer metabolism[J/OL]. Polymers, 2023, 15(4): 976[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/36850263/. DOI:10.3390/polym15040976.

[15] JAIN S, WANG X, CHANG C C, et al. Src inhibition blocks c-myc translation and glucose metabolism to prevent the development of breast cancer[J]. Cancer Res, 2015, 75(22): 4863-4875. DOI:10.1158/0008-5472.CAN-14-2345.

[16] YANG W L, WEI Y Z, WANG T, et al. Cytoplasmic localization of SETDB1-induced Warburg effect via c-MYC-LDHA axis enhances migration and invasion in breast carcinoma[J/OL]. Int J Mol Med, 2024, 53(4): 40[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/38426579/. DOI:10.3892/ijmm.2024.5364.

[17] JIAO L, WANG S Q, ZHENG Y F, et al. Betulinic acid suppresses breast cancer aerobic glycolysis via caveolin-1/NF-κB/c-Myc pathway [J]. Biochem Pharmacol, 2019, 161: 149-162. DOI: 10.1016/j.bcp.2019.01.016.

[18] LI R Q, MEI S C, DING Q, et al. A pan-cancer analysis of the role of hexokinase II (HK2) in human tumors[J/OL]. Sci Rep, 2022, 12(1): 18807[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/36335239/. DOI:10.1038/s41598-022-23598-8.

[19] BLAHA C S, RAMAKRISHNAN G, JEON S M, et al. A non-catalytic scaffolding activity of hexokinase 2 contributes to EMT and metastasis[J/OL]. Nat Commun, 2022, 13(1): 899[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/35173161/. DOI:10.1038/s41467-022-28440-3.

[20] LIU C, LI S J, ZHANG X X, et al. Nogo-B receptor increases glycolysis and the paclitaxel resistance of estrogen receptor-positive breast cancer via the HIF-1α-dependent pathway[J]. Cancer Gene Ther, 2023, 30(5): 647-658. DOI:10.1038/s41417-022-00542-6.

[21] YANG Z T, ZHANG C Y, LIU X Z, et al. SETD5 regulates glycolysis in breast cancer stem-like cells and fuels tumor growth[J]. Am J Pathol, 2022, 192(4): 712-721. DOI:10.1016/j.ajpath.2021.12.006.

[22] ZHAO L, KANG M, LIU X M, et al. UBR7 inhibits HCC tumorigenesis by targeting Keap1/Nrf2/Bach1/HK2 and glycolysis [J/OL]. J Exp Clin Cancer Res, 2022, 41(1): 330 [2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/36419136/. DOI:10.1186/s13046-022-02528-6.

[23] ZHANG T, ZHU X Y, WU H C, et al. Targeting the ROS/PI3K/AKT/HIF-1α/HK2 axis of breast cancer cells: Combined administration of Polydatin and 2-Deoxy-d-glucose[J]. J Cell Mol Med, 2019, 23(5): 3711-3723. DOI:10.1111/jcmm.14276.

[24] JUSZCZAK K, KUBICKA A, KITEL R, et al. Hexokinase 2 inhibition and biological effects of BNBZ and its derivatives: the influence of the number and arrangement of hydroxyl groups

[J/OL]. Int J Mol Sci, 2022, 23(5): 2616[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/35269760/. DOI:10.3390/ijms23052616.

[25] LEE H J, LI C F, RUAN D E, et al. Non-proteolytic ubiquitination of Hexokinase 2 by HectH9 controls tumor metabolism and cancer stem cell expansion[J/OL]. Nat Commun, 2019, 10(1): 2625[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/31201299/. DOI:10.1038/s41467-019-10374-y.

[26] CHANDRIKA M, CHUA P J, MUNIASAMY U, et al. Prognostic significance of phosphoglycerate dehydrogenase in breast cancer[J]. Breast Cancer Res Treat, 2021, 186(3): 655-665. DOI: 10.1007/s10549-021-06123-9.

[27] SHARIF T, MARTELL E, DAI C, et al. Phosphoglycerate dehydrogenase inhibition induces p-mTOR-independent autophagy and promotes multilineage differentiation in embryonal carcinoma stem-like cells[J/OL]. Cell Death Dis, 2018, 9(10): 990[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/30250195/. DOI: 10.1038/s41419-018-0997-8.

[28] CHEN C, ZHU T Y, LIU X Q, et al. Identification of a novel PHGDH covalent inhibitor by chemical proteomics and phenotypic profiling[J]. Acta Pharm Sin B, 2022, 12(1): 246-261. DOI:10.1016/j.apsb.2021.06.008.

[29] PATRICK MURPHY J, GIACOMANTONIO M A, PAULO J A, et al. The NAD$^+$ salvage pathway supports PHGDH-driven serine biosynthesis[J]. Cell Rep, 2018, 24(9): 2381-2391.e5. DOI:10.1016/j.celrep.2018.07.086.

[30] LIU J, ZHANG C, WU H, et al. Parkin ubiquitinates phosphoglycerate dehydrogenase to suppress serine synthesis and tumor progression[J]. J Clin Invest, 2020, 130(6): 3253-3269. DOI: 10.1172/JCI132876.

[31] LEE Y B, MIN J K, KIM J G, et al. Multiple functions of pyruvate kinase M2 in various cell types[J]. J Cell Physiol, 2022, 237(1): 128-148. DOI:10.1002/jcp.30536.

[32] CHEN X, CHEN S W, YU D S. Protein kinase function of pyruvate kinase M2 and cancer[J/OL]. Cancer Cell Int, 2020, 20(1): 523 [2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/33292198/. DOI: 10.1186/s12935-020-01612-1.

[33] ZAHRA K, DEY T, ASHISH, et al. Pyruvate kinase M2 and cancer: the role of PKM2 in promoting tumorigenesis[J/OL]. Front Oncol, 2020, 10: 159[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/32195169/. DOI:10.3389/fonc.2020.00159.

[34] YU P, LI A X, CHEN X S, et al. PKM2-c-myc-survivin cascade regulates the cell proliferation, migration, and tamoxifen resistance in breast cancer[J/OL]. Front Pharmacol, 2020, 11: 550469[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/33013387/. DOI:10.3389/fphar.2020.550469.

[35] YAO X M, LI W, LI L Q, et al. YTHDF1 upregulation mediates hypoxia-dependent breast cancer growth and metastasis through regulating PKM2 to affect glycolysis[J/OL]. Cell Death Dis, 2022, 13 (3): 258[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/35319018/. DOI:10.1038/s41419-022-04711-1.

[36] ABEYWARDANA T, OH M, JIANG L, et al. CARM1 suppresses de novo serine synthesis by promoting PKM2 activity[J]. J Biol Chem, 2018, 293(39): 15290-15303. DOI:10.1074/jbc.RA118.004512.

[37] SRIVASTAVA D, NANDI S, DEY M. Mechanistic and structural insights into cysteine-mediated inhibition of pyruvate kinase muscle

isoform 2[J]. Biochemistry, 2019, 58(35): 3669-3682. DOI:10.1021/acs.biochem.9b00349.

[38] APOSTOLIDI M, VATHIOTIS I A, MUTHUSAMY V, *et al*. Targeting pyruvate kinase M2 phosphorylation reverses aggressive cancer phenotypes[J]. Cancer Res, 2021, 81(16): 4346-4359. DOI: 10.1158/0008-5472.CAN-20-4190.

[39] YU H, WANG M, ZHANG T, *et al*. Dual roles of β-arrestin 1 in mediating cell metabolism and proliferation in gastric cancer[J/OL]. Proc Natl Acad Sci USA, 2022, 119(40): e2123231119[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/36161910/. DOI: 10.1073/pnas.2123231119.

[40] LUKER K E, LUKER G D. The CXCL12/CXCR4/ACKR3 signaling axis regulates PKM2 and glycolysis[J/OL]. Cells, 2022, 11(11): 1775 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/35681470/. DOI: 10.3390/cells11111775.

[41] SHARMA D, SINGH M, RANI R. Role of LDH in tumor glycolysis: regulation of LDHA by small molecules for cancer therapeutics[J]. Semin Cancer Biol, 2022, 87: 184-195. DOI: 10.1016/j.semcancer.2022.11.007.

[42] LIU J, LI Y, CHEN X Q, *et al*. rs11046147 mutation in the promoter region of lactate dehydrogenase-B as a potential predictor of prognosis in triple-negative breast cancer[J]. Cancer Commun, 2020, 40(6): 279-282. DOI:10.1002/cac2.12031.

[43] KHAJAH M A, KHUSHAISH S, LUQMANI Y A. Lactate dehydrogenase A or B knockdown reduces lactate production and inhibits breast cancer cell motility *in vitro*[J/OL]. Front Pharmacol, 2021, 12: 747001[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/34744727/. DOI:10.3389/fphar.2021.747001.

[44] NAIK A, DECOCK J. Targeting of lactate dehydrogenase C dysregulates the cell cycle and sensitizes breast cancer cells to DNA damage response targeted therapy[J]. Mol Oncol, 2022, 16(4): 885-903. DOI:10.1002/1878-0261.13024.

[45] CHEN X M, LUO R, ZHANG Y M, *et al*. Long noncoding RNA DIO$_3$OS induces glycolytic-dominant metabolic reprogramming to promote aromatase inhibitor resistance in breast cancer[J/OL]. Nat Commun, 2022, 13(1): 7160[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/36418319/. DOI:10.1038/s41467-022-34702-x.

[46] GUDDETI R K, THOMAS L, KANNAN A, *et al*. The chromatin modifier MORC2 affects glucose metabolism by regulating the expression of lactate dehydrogenase A through a feed forward loop with c-Myc[J]. FEBS Lett, 2021, 595(9): 1289-1302. DOI:10.1002/1873-3468.14062.

[47] MUNG K L, MEINANDER A, KOSKINEN P J. PIM kinases phosphorylate lactate dehydrogenase A at serine 161 and suppress its nuclear ubiquitination[J]. FEBS J, 2023, 290(9): 2489-2502. DOI:10.1111/febs.16653.

[48] ZHOU Y, NIU W H, LUO Y W, *et al*. p53/Lactate dehydrogenase A axis negatively regulates aerobic glycolysis and tumor progression in breast cancer expressing wild-type p53[J]. Cancer Sci, 2019, 110 (3): 939-949. DOI:10.1111/cas.13928.

[49] ROSSO M, LAPYCKYJ L, BESSO M J, *et al*. Characterization of the molecular changes associated with the overexpression of a novel epithelial cadherin splice variant mRNA in a breast cancer model using proteomics and bioinformatics approaches: identification of changes in cell metabolism and an increased

expression of lactate dehydrogenase B[J/OL]. Cancer Metab, 2019, 7: 5 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/31086659/. DOI:10.1186/s40170-019-0196-9.

[50] FRANK A C, RAUE R, FUHRMANN D C, *et al*. Lactate dehydrogenase B regulates macrophage metabolism in the tumor microenvironment[J]. Theranostics, 2021, 11(15): 7570-7588. DOI: 10.7150/thno.58380.

[51] YANG Y, MA X, LI Y, *et al*. The evolving tumor-associated adipose tissue microenvironment in breast cancer: from cancer initiation to metastatic outgrowth[J]. Clin Transl Oncol, 2025, 27(7): 2778-2788. DOI:10.1007/s12094-024-03831-8.

[52] CHANG Y, DU R, XIA F, *et al*. Dysregulation of fatty acid metabolism in breast cancer and its targeted therapy[J]. Breast Cancer, 2024, 16: 825-844. DOI:10.2147/BCTT.S496322.

[53] FENG W W, WILKINS O, BANG S, *et al*. CD36-mediated metabolic rewiring of breast cancer cells promotes resistance to HER2-targeted therapies[J]. Cell Rep, 2019, 29(11): 3405-3420. DOI:10.1016/j.celrep.2019.11.008.

[54] GYAMFI J, YEO J H, KWON D, *et al*. Interaction between CD36 and FABP4 modulates adipocyte-induced fatty acid import and metabolism in breast cancer[J/OL]. NPJ Breast Cancer, 2021, 7(1): 129[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/34561446/. DOI: 10.1038/s41523-021-00324-7.

[55] LUIS G, GODFROID A, NISHIUMI S, *et al*. Tumor resistance to ferroptosis driven by stearoyl-CoA desaturase-1 (SCD1) in cancer cells and fatty acid biding protein-4 (FABP4) in tumor microenvironment promote tumor recurrence[J/OL]. Redox Biol, 2021, 43: 102006[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/34030117/. DOI:10.1016/j.redox.2021.102006.

[56] BIAN H T, LIANG X H, LU D, *et al*. In silico discovery of stapled peptide inhibitor targeting the Nur77-PPARγ interaction and its anti-breast-cancer efficacy[J/OL]. Adv Sci, 2024, 11(26): e2308435 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/38682467/. DOI: 10.1002/advs.202308435.

[57] YANG P B, HOU P P, HOU P P, *et al*. Blocking PPARγ interaction facilitates Nur77 interdiction of fatty acid uptake and suppresses breast cancer progression[J]. Proc Natl Acad Sci USA, 2020, 117 (44): 27412-27422. DOI:10.1073/pnas.2002997117.

[58] FENG X F, ZHANG M, WANG B, *et al*. CRABP2 regulates invasion and metastasis of breast cancer through hippo pathway dependent on ER status[J/OL]. J Exp Clin Cancer Res, 2019, 38(1): 361[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/31419991/. DOI: 10.1186/s13046-019-1345-2.

[59] HATIPOGLU A, MENON D, LEVY T, *et al*. Inhibiting glutamine utilization creates a synthetic lethality for suppression of ATP citrate lyase in KRas-driven cancer cells[J/OL]. PLoS One, 2022, 17 (10): e0276579[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/36269753/. DOI:10.1371/journal.pone.0276579.

[60] LEE H, ZANDKARIMI F, ZHANG Y L, *et al*. Energy-stress-mediated AMPK activation inhibits ferroptosis[J]. Nat Cell Biol, 2020, 22(2): 225-234. DOI:10.1038/s41556-020-0461-8.

[61] YANG J H, KIM N H, YUN J S, *et al*. Snail augments fatty acid oxidation by suppression of mitochondrial ACC2 during cancer progression[J/OL]. Life Sci Alliance, 2020, 3(7): e202000683 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/32487689/. DOI:

10.26508/lsa.202000683.

[62] MAURO L, NAIMO G D, GELSOMINO L, *et al*. Uncoupling effects of estrogen receptor α on LKB1/AMPK interaction upon adiponectin exposure in breast cancer[J]. FASEB J, 2018, 32(8): 4343-4355. DOI:10.1096/fj.201701315R.

[63] KIM D H, SONG N Y, YIM H. Targeting dysregulated lipid metabolism in the tumor microenvironment[J]. Arch Pharm Res, 2023, 46(11/12): 855-881. DOI:10.1007/s12272-023-01473-y.

[64] BRUNING U, MORALES-RODRIGUEZ F, KALUCKA J, *et al*. Impairment of angiogenesis by fatty acid synthase inhibition involves mTOR malonylation[J]. Cell Metab, 2018, 28(6): 866-880. DOI:10.1016/j.cmet.2018.07.019.

[65] FERRARO G B, ALI A, LUENGO A, *et al*. Fatty acid synthesis is required for breast cancer brain metastasis[J]. Nat Cancer, 2021, 2 (4): 414-428. DOI:10.1038/s43018-021-00183-y.

[66] SCHROEDER B, VANDER STEEN T, ESPINOZA I, *et al*. Fatty acid synthase (FASN) regulates the mitochondrial priming of cancer cells[J/OL]. Cell Death Dis, 2021, 12(11): 977[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/34675185/. DOI: 10.1038/s41419-021-04262-x.

[67] MENENDEZ J A, PAPADIMITROPOULOU A, VANDER STEEN T, et al. Fatty acid synthase confers tamoxifen resistance to ER[+]/HER2^{+} breast cancer[J/OL]. Cancers, 2021, 13(5): 1132[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/33800852/. DOI: 10.3390/cancers13051132.

[68] XIE P, PENG Z Q, CHEN Y J, *et al*. Neddylation of PTEN regulates its nuclear import and promotes tumor development[J]. Cell Res, 2021, 31(3): 291-311. DOI:10.1038/s41422-020-00443-z.

[69] CHENG C M, GENG F, CHENG X, *et al*. Lipid metabolism reprogramming and its potential targets in cancer[J/OL]. Cancer Commun, 2018, 38(1): 27[2025-07-15]. https://pubmed. ncbi. nlm. nih.gov/29784041/. DOI:10.1186/s40880-018-0301-4.

[70] JIE Z W, XIE Z A, XU W B, *et al*. SREBP-2 aggravates breast cancer associated osteolysis by promoting osteoclastogenesis and breast cancer metastasis[J]. Biochim Biophys Acta Mol Basis Dis, 2019, 1865(1): 115-125. DOI:10.1016/j.bbadis.2018.10.026.

[71] PHAM D V, TILIJA PUN N, PARK P H. Autophagy activation and SREBP-1 induction contribute to fatty acid metabolic reprogramming by leptin in breast cancer cells[J]. Mol Oncol, 2021, 15(2): 657-678. DOI:10.1002/1878-0261.12860.

[72] ZHAO Y, LI H, ZHANG Y Y, *et al*. Oncoprotein HBXIP modulates abnormal lipid metabolism and growth of breast cancer cells by activating the LXRs/SREBP-1c/FAS signaling cascade[J]. Cancer Res, 2016, 76(16): 4696-4707. DOI:10.1158/0008-5472. CAN-15-1734.

[73] YI J M, ZHU J J, WU J, *et al.* Oncogenic activation of PI3K-AKT-mTOR signaling suppresses ferroptosis *via* SREBP-mediated lipogenesis[J]. Proc Natl Acad Sci USA, 2020, 117(49): 31189-31197. DOI:10.1073/pnas.2017152117.

[74] LOO S Y, TOH L P, XIE W H, *et al*. Fatty acid oxidation is a druggable gateway regulating cellular plasticity for driving metastasis in breast cancer[J/OL]. Sci Adv, 2021, 7(41): eabh2443 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/34613780/. DOI: 10.1126/sciadv.abh2443.

[75] LI Y J, FAHRMANN J F, AFTABIZADEH M, *et al*. Fatty acid

oxidation protects cancer cells from apoptosis by increasing mitochondrial membrane lipids[J/OL]. Cell Rep, 2022, 39(9): 110870[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/35649368/. DOI:10.1016/j.celrep.2022.110870.

[76] LU R P, HONG J J, FU T, *et al*. Loss of OVOL2 in triple-negative breast cancer promotes fatty acid oxidation fueling stemness characteristics[J/OL]. Adv Sci, 2024, 11(24): e2308945[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/38627980/. DOI: 10.1002/advs.202308945.

[77] WANG T Y, FAHRMANN J F, LEE H,*et al.* JAK/STAT3-regulated fatty acid β-oxidation is critical for breast cancer stem cell self-renewal and chemoresistance[J]. Cell Metab, 2018, 27(1): 136-150. DOI:10.1016/j.cmet.2017.11.001.

[78] YU J, DU Y J, LIU C, *et al*. Low GPR81 in ER[+] breast cancer cells drives tamoxifen resistance through inducing PPARα -mediated fatty acid oxidation[J/OL]. Life Sci, 2024, 350: 122763[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/38823505/. DOI: 10.1016/j.lfs.2024.122763.

[79] QUEK L E, VAN GELDERMALSEN M, GUAN Y F, *et al*. Glutamine addiction promotes glucose oxidation in triple-negative breast cancer[J]. Oncogene, 2022, 41(34): 4066-4078. DOI:10.1038/s41388-022-02408-5.

[80] KORANGATH P, TEO W W, SADIK H, *et al*. Targeting glutamine metabolism in breast cancer with aminooxyacetate[J]. Clin Cancer Res, 2015, 21(14): 3263-3273. DOI:10.1158/1078-0432. CCR-14-1200.

[81] NAN D, YAO W P, HUANG L L, *et al*. Glutamine and cancer: metabolism, immune microenvironment, and therapeutic targets[J/OL]. Cell Commun Signal, 2025, 23(1): 45 [2025-07-15]. https://pubmed. ncbi.nlm.nih.gov/39856712/. DOI:10.1186/s12964-024-02018-6.

[82] VAN GELDERMALSEN M, WANG Q, NAGARAJAH R, *et al*. ASCT2/SLC1A5 controls glutamine uptake and tumour growth in triple-negative basal-like breast cancer[J]. Oncogene, 2016, 35(24): 3201-3208. DOI:10.1038/onc.2015.381.

[83] YOO H C, YU Y C, SUNG Y, *et al*. Glutamine reliance in cell metabolism[J]. Exp Mol Med, 2020, 52(9): 1496-1516. DOI: 10.1038/s12276-020-00504-8.

[84] ZHOU Q Y, LIN W Y, WANG C Q, *et al*. Neddylation inhibition induces glutamine uptake and metabolism by targeting CRL3[SPOP] E3 ligase in cancer cells[J/OL]. Nat Commun, 2022, 13(1): 3034[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/35641493/. DOI:10.1038/s41467-022-30559-2.

[85] TORRINO S, GRASSET E M, AUDEBERT S, *et al*. Mechano-induced cell metabolism promotes microtubule glutamylation to force metastasis[J]. Cell Metab, 2021, 33(7): 1342-1357. DOI: 10.1016/j.cmet.2021.05.009.

[86] TAN Z Q, BOYAPATI K, TRESSLER C M, *et al*. Glutamine transporter SLC38A3 promotes breast cancer metastasis *via* Gsk3β/β -catenin/EMT pathway[J/OL]. Cancer Lett, 2024, 586: 216653 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/38309615/. DOI: 10.1016/j.canlet.2024.216653.

[87] MESTRE-FARRERA A, BRUCH-OMS M, PEÑA R, *et al*. Glutamine-directed migration of cancer-activated fibroblasts facilitates epithelial tumor invasion[J]. Cancer Res, 2021, 81(2): 438-451. DOI:10.1158/0008-5472.CAN-20-0622.

[88] KAY E J, PATERSON K, RIERA-DOMINGO C, et al. Cancer-associated fibroblasts require proline synthesis by PYCR1 for the deposition of pro-tumorigenic extracellular matrix[J]. Nat Metab, 2022, 4(6): 693-710. DOI:10.1038/s42255-022-00582-0.

[89] TANG Y X, WANG S Q, LI Y, et al. Simultaneous glutamine metabolism and PD-L1 inhibition to enhance suppression of triple-negative breast cancer[J/OL]. J Nanobiotechnology, 2022, 20(1): 216[2025-07-15]. https://pubmed.ncbi.nlm.nih.gov/35524267/. DOI: 10.1186/s12951-022-01424-7.

[90] EDWARDS D N, NGWA V M, RAYBUCK A L, et al. Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer[J/OL]. J Clin Invest, 2021, 131(4): e140100[2025-07-15]. https://pubmed. ncbi. nlm.nih.gov/33320840/. DOI:10.1172/JCI140100.

[91] HUANG G Y, WU Y J, GAN H C, et al. Overexpression of CD2/ CD27 could inhibit the activation of nitrogen metabolism pathways and suppress M2 polarization of macrophages, thereby preventing brain metastasis of breast cancer[J/OL]. Transl Oncol, 2023, 37: 101768[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/37666207/. DOI:10.1016/j.tranon.2023.101768.

[92] SHEN X W, WANG G G, HE H, et al. SLC38A5 promotes glutamine metabolism and inhibits cisplatin chemosensitivity in breast cancer[J]. Breast Cancer, 2024, 31(1): 96-104. DOI:10.1007/ s12282-023-01516-8.

[93] MOROTTI M, ZOIS C E, EL-ANSARI R, et al. Increased expression of glutamine transporter SNAT2/SLC38A2 promotes glutamine dependence and oxidative stress resistance, and is associated with worse prognosis in triple-negative breast cancer[J]. Br J Cancer, 2021, 124(2): 494-505. DOI: 10.1038/s41416-020-01113-y.

[94] YING M F, YOU D, ZHU X B, et al. Lactate and glutamine support NADPH generation in cancer cells under glucose deprived conditions [J/OL]. Redox Biol, 2021, 46: 102065[2025-07-15]. https://pubmed. ncbi.nlm.nih.gov/34293554/. DOI:10.1016/j.redox.2021.102065.

[95] JAGGUPILLI A, LY S, NGUYEN K, et al. Metabolic stress induces GD2$^+$ cancer stem cell-like phenotype in triple-negative breast cancer[J]. Br J Cancer, 2022, 126(4): 615-627. DOI:10.1038/ s41416-021-01636-y.

[96] PREMARATNE A, HO C, BASU S, et al. Liver X receptor inverse agonist GAC0001E5 impedes glutaminolysis and disrupts redox homeostasis in breast cancer cells[J/OL]. Biomolecules, 2023, 13 (2): 345[2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/36830714/. DOI:10.3390/biom13020345.

[97] VERNIER M, DUFOUR C R, MCGUIRK S, et al. Estrogen-related receptors are targetable ROS sensors[J]. Genes Dev, 2020, 34(7/8): 544-559. DOI:10.1101/gad.330746.119.

[98] VILLAGRAN M, FERREIRA J, MARTORELL M, et al. The role of vitamin C in cancer prevention and therapy: a literature review[J/OL]. Antioxidants, 2021, 10(12): 1894[2025-07-15]. https://pubmed.ncbi. nlm.nih.gov/34942996/. DOI:10.3390/antiox10121894.

[99] MARIC T, BAZHIN A, KHODAKIVSKYI P, et al. A bioluminescent-based probe for in vivo non-invasive monitoring of nicotinamide riboside uptake reveals a link between metastasis and NAD$^+$ metabolism[J/OL]. Biosens Bioelectron, 2023, 220: 114826 [2025-07-15]. https://pubmed. ncbi. nlm. nih. gov/36371959/. DOI: 10.1016/j.bios.2022.114826.

[100] RANA N K, SINGH P, KOCH B. CoCl$_2$ simulated hypoxia induce cell proliferation and alter the expression pattern of hypoxia associated genes involved in angiogenesis and apoptosis[J/OL]. Biol Res, 2019, 52(1): 12[2025-07-15]. https://pubmed. ncbi. nlm. nih.gov/30876462/. DOI:10.1186/s40659-019-0221-z.