中国科学: 生命科学 2026 年 第 56 卷 第 7 期: 1716 ~ 1727
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《中国科学》杂志社 SCIENCE CHINA PRESS
评 述 青年科学家专栏

奶牛肝脏糖异生调控机制的研究进展

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收稿日期: 2025-11-21; 接受日期: 2026-02-13; 网络版发表日期: 2026-05-29
国家自然科学基金(批准号: 32422082)资助

摘要 葡萄糖是乳汁合成的核心能量底物和乳糖合成的基本结构单元, 其供给水平直接决定奶牛的产奶效率. 然而, 奶牛独特的瘤胃微生物发酵特性导致日粮中大量葡萄糖被分解为挥发性脂肪酸, 使得体内80%以上的葡萄糖依赖肝脏糖异生途径合成. 因此, 深入解析奶牛肝脏糖异生的调控机制, 是保障奶牛健康高效生产的关键科学问题. 本文围绕奶牛肝脏糖异生展开系统综述, 首先从肝脏结构与功能分区入手, 明确门静脉区和中央静脉区是执行糖异生功能的主要细胞群; 其次, 探讨肝脏糖异生的底物偏好性, 阐明丙酸作为成年奶牛肝脏糖异生最主要的碳源, 其贡献度高达60%~74%; 再次, 详细综述糖异生调控元件, 绘制出cAMP的效应元件结合蛋白(cAMP-response element binding protein, CREB)、叉头框转录因子1(forkhead transcription factor O1, FOXO1)、过氧化物酶体增殖激活受体-γ辅激活因子-1α(peroxisome proliferator-activated receptor γ coactivator 1-alpha, PGC-1α)、肝细胞核因子4α(hepatic nuclear factor 4 alpha, HNF4α)等多个转录因子协同作用的调控网络; 最后, 针对当前研究现状对该领域未来研究方向进行展望, 旨在为改善奶牛葡萄糖代谢水平、提升生产性能提供理论依据与技术支撑.

关键词 奶牛, 肝脏糖异生, 调控机制, 产奶性能

葡萄糖既是乳汁合成的主要能量底物, 也是乳糖形成的基本结构单元, 其巨大的需求量源于乳糖在乳腺泌乳过程中的重要作用. 研究表明, 每生产1 kg牛奶, 乳腺需消耗70 g葡萄糖用于合成乳糖[1,2], 这意味着一头日产40 kg奶的高产奶牛, 仅合成乳糖每天就需要消耗2.8 kg以上的葡萄糖. 乳糖作为乳汁中的主要碳水化合物, 由一分子葡萄糖和一分子半乳糖构成(后者同样由葡萄糖转化而来). 研究表明, 乳糖通过维持乳腺上皮细胞内的渗透压来调控乳汁分泌量. 本团队[3]的前期研究证实, 在不同物种的乳汁中, 乳糖含量与含水量存在显著正相关. 此外, 向奶山羊乳腺动脉灌注葡萄糖的实验也表明, 葡萄糖供给量的增加能够协同提升乳糖合成速率和产奶量[4]. 这些研究共同确证了乳糖合成是产奶效率的限速环节, 因此, 葡萄糖的有效供给是调控产奶性能的关键靶点. 除作为合成底物外, 葡萄糖还是乳腺上皮细胞自身代谢活动不可或缺的能量来源. 因此, 如何在确保奶牛健康的前提下, 最大限度地提高奶牛乳糖合成效率, 是提升产奶性能的核心科学问题.

然而, 反刍动物独特的瘤胃发酵生理结构决定了其无法直接从日粮中获得大量葡萄糖, 必须高度依赖内源性的糖异生[5,6]. 研究表明, 肝脏糖异生提供的葡

引用格式: 王国艳, 谯锦锐, 王江新, 等. 奶牛肝脏糖异生调控机制的研究进展. 中国科学: 生命科学, 2026, 56: 1716–1727
Wang G Y, Qiao J R, Wang J X, et al. Research progress on the regulatory mechanisms of gluconeogenesis in the liver of dairy cows (in Chinese). Sci Sin Vitae, 2026, 56: 1716–1727, doi: 10.1360/SSV-2025-0380

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https://www.sciengine.com/doi/10.1360/SSV-2025-0380

葡萄糖占奶牛总葡萄糖周转量的80%以上[7,8]. 奶牛糖异生的前体物质主要包括丙酸、氨基酸、甘油和乳酸. 其中, 丙酸是成年奶牛最主要的糖异生碳源, 而在瘤胃尚未发育完全的胎牛或者犊牛阶段, 乳酸则是其重要的糖异生前体. 因此, 在现代集约化饲养体系中, 通过精准营养调控以优化瘤胃发酵模式、增加丙酸产量, 是满足泌乳牛巨大葡萄糖需求, 从而保障其高产性能、健康状况及养殖经济效益的核心措施. 本文将基于已有研究, 系统阐述奶牛肝脏糖异生的分子调控途径, 并总结展望未来的研究方向, 以期为优化奶牛葡萄糖代谢及提升奶产量提供理论依据.

1 肝脏结构和功能

肝脏是哺乳动物体内的糖脂代谢调控中心, 兼具内分泌和外分泌功能, 还参与免疫调节, 在维持哺乳动物生理稳态中不可或缺[9]. 肝脏的功能与结构紧密相关, 由规则排列的肝小叶组成. 肝小叶横切面呈六边形, 六个角各有一组“门三联管”, 由肝动脉、门静脉和肝内胆管构成, 中央为中央静脉(图1)[10,11]. 肝实质细胞是主要功能细胞, 在中央静脉与门三联管之间呈索状排列, 占肝脏细胞总数的60%、体积的80%以上[12]. 肝实质细胞通过与具有孔状结构的毛细血管内皮细胞紧密互作, 实现与血液的高效物质交换; 同时形成胆小管, 分泌胆汁(图1). 除了肝实质细胞、胆管细胞和内皮细胞, 肝脏还包含间皮细胞、肝星状细胞、库普弗细胞、间充质细胞及大量血细胞(图1). 因此, 肝脏功能的正常执行, 是其内部各类细胞形成的特定空间结构及细胞间高度协同作用的结果[13].

肝脏存在明显的结构和功能分区[14]. 肝实质细胞虽形态均一, 但功能沿门静脉至中央静脉呈现明确分工: 门静脉区(Zone 1)主导糖异生与脂肪酸氧化; 中央静脉区(Zone 3)主要负责糖酵解、脂质合成及药物解毒[15]; 肝小叶中部的肝实质细胞(Zone 2)则负责肝细胞的再生[16~18]. 这种功能梯度是肝脏高效生理活动和稳态维持的基础. 最近的单细胞研究表明, 肝实质细胞的糖异生活性表现出显著的空间和时间可塑性: 在进食状态下肝脏整体的糖异生活性较低; 在初始禁食期间, 门静脉周围肝实质细胞(Zone 1)的糖异生活性逐渐增加; 然而, 随着禁食的进行, 中央静脉周围肝实质细胞(Zone 3)的糖异生活性也逐渐增加; 在进入饥饿状态后, Zone 3表现出与Zone 1相似的糖异生活性[19]. 该结果表明, 奶牛在能量负平衡状态下, 特别是在围产期阶段, 肝脏不同区域的代谢分工可能趋向整合与协同, 从而增强整体糖异生能力, 缓解能量负平衡所带来的生理压力.

2 糖异生的底物和过程

糖异生作为哺乳动物维持血糖稳态的关键生理过程, 在不同物种间, 其底物选择与活性水平随物种的进化适应、饮食结构和代谢需求而异(图2). 杂食性哺乳动物(如人类、猪、小鼠)在进食状态下血糖主要来自肠道葡萄糖吸收, 糖异生在禁食状态下才发挥关键作用, 其底物主要是氨基酸和乳酸[20], 另有研究表明, 小鼠禁食期间可利用丙酸合成葡萄糖[21]. 肉食性与海洋哺乳动物(如猫、海豹)摄食结构以蛋白质和脂肪为主, 维持了持续高水平的糖异生能力, 利用乳酸、甘油、氨基酸作为糖异生的底物, 以维持血糖水平[22,23]. 此外, 非反刍草食动物(如马)作为后肠发酵者, 糖异生能力介于反刍动物和单胃动物之间, 主要依赖丙酸, 同时也利用甘油和氨基酸[24].

与前述哺乳动物相比, 反刍动物(如牛、羊)因瘤胃微生物对日粮碳水化合物的代谢, 肝脏持续进行的糖异生成为机体内源性葡萄糖的主要来源[8,25]. 因此, 提高肝脏糖异生被视为提升奶产量的有效途径[26].

丙酸作为反刍动物肝脏糖异生的主要底物, 能提供60%~74%的碳源[27,28]. 此外, 肝脏还能利用生糖氨基酸经糖异生转化为丙酮酸或草酰乙酸进入糖异生途径(图2), 氨基酸提供的碳源占反刍动物糖异生碳源的11%~16%[8]. 围产期奶牛还可将甘油作为糖异生的底物[29]. 胎牛对丙酸的利用效率较低, 糖异生底物以乳酸和氨基酸为主[30]. 实验证据表明, 乳酸为胎牛提供了49%的葡萄糖[31], 且随着小牛和羔羊等的发育成熟, 肝脏利用乳酸进行糖异生的能力逐渐下降[32]. 氨基酸对肝脏糖异生的贡献约为25%[33,34], 其中丙氨酸和谷氨酸提供的葡萄糖比例分别为25%和15%, 天冬氨酸、甘氨酸和丝氨酸的比例约为5%~7%[34]. 研究显示, 外源性氨基酸输注可提高妊娠绵羊肝脏葡萄糖的生成, 并促进糖异生相关基因磷酸烯醇式丙酮酸羧激酶1 (phosphoenolpyruvate carboxy kinase 1, *PCK1*)和葡萄糖-6-磷酸酶(glucose-6-phosphatase, *G6PC*)的表达[35].

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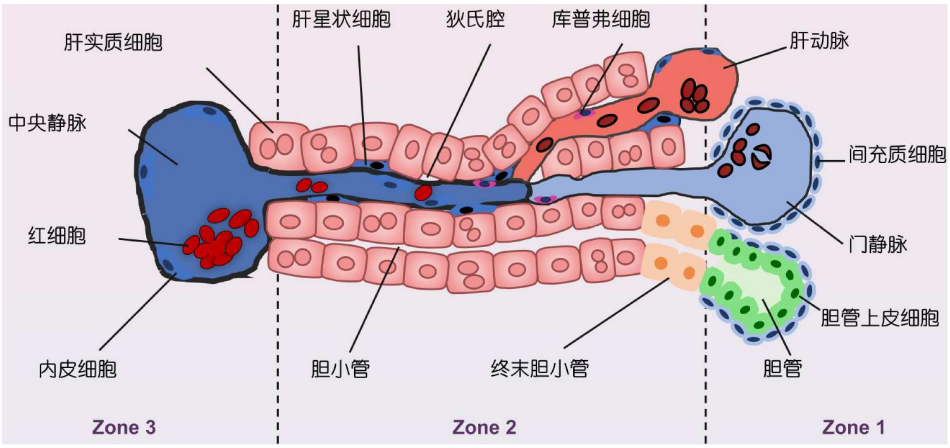


图 1 肝脏的结构和分区(图片修改自文献[11])
Figure 1 Structure and zonation of the liver (adapted from ref. [11])

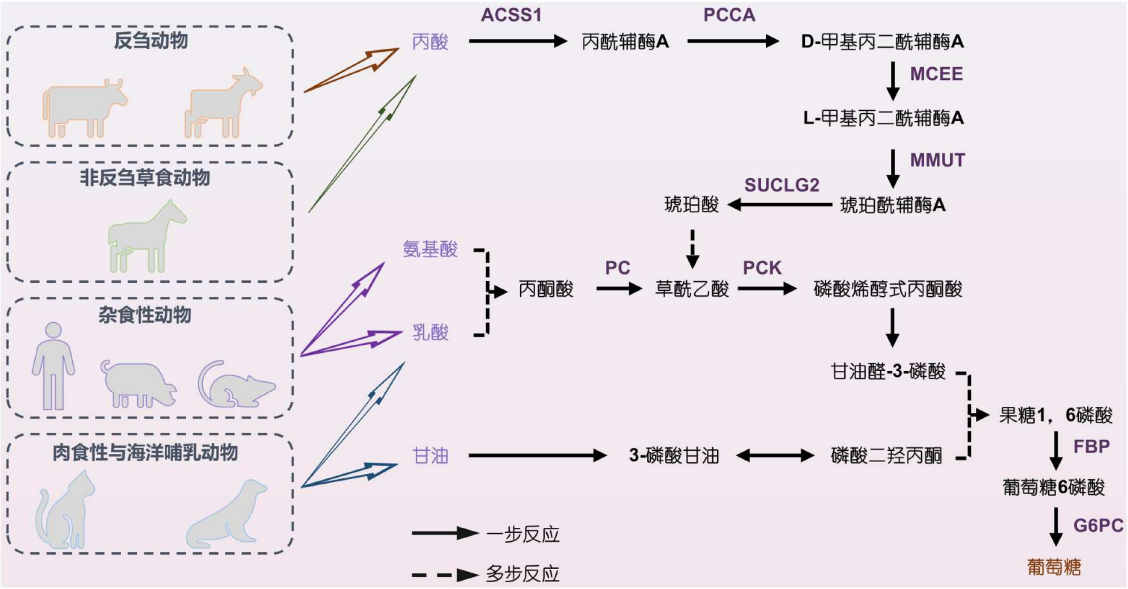


图 2 糖异生的底物和过程
Figure 2 Substrates and process of gluconeogenesis

此外，丙酸处理奶牛肝脏细胞可显著提高培养基中葡萄糖的含量，同时提升PCK和G6PC的表达和活性[36,37].

糖异生在大部分反应上与糖酵解呈逆向关系，但通过三个旁路反应绕过糖酵解的不可逆步骤，由PCK、果糖-1,6-二磷酸酶(fructose1,6-bisphosphatase，FBP1)和G6PC等限速酶驱动[38,39]. 在反刍动物中，丙酸是糖异生的主要前体，其代谢途径首先发生在线粒体内: 丙酸在乙酰辅酶A合成酶(acyl-CoA synthetase short chain family member 1, ACSS1)的作用下形成丙酰辅酶A，随后在丙酰辅酶A羧化酶(propionyl-CoA carboxylase, PCCA)的催化下形成甲基丙二酰辅酶A，再经甲基丙二酰辅酶A异构酶(methyl malonyl-CoA epimerase, MCEE)和甲基丙二酰辅酶A变位酶(methylmalonyl-CoA mutase, MMUT)转化成琥珀酰辅酶A，然后由琥珀酰辅酶A合成酶(succinate-CoA ligase GDP-forming subunit beta, SUCLG2)转化为琥珀酸后进入三羧酸循环生成草酰乙酸[40]. 线粒体内生成的草酰乙酸主要由

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线粒体型PCK2催化生成磷酸烯醇式丙酮酸, 随后进入细胞质基质. 而胞质型PCK1主要负责来源于细胞质基质的草酰乙酸的转化反应. 已有研究表明, 缺乏PCK2的肝细胞在利用乳酸、丙氨酸和谷氨酰胺作为底物时糖异生速率显著降低, 而利用丙酮酸和甘油时未见明显变化[41]. 这说明PCK2在丙酸、乳酸和生糖氨基酸转化成草酰乙酸的过程中发挥关键作用. 最终, 磷酸烯醇式丙酮酸经一系列酶促反应生成葡萄糖-6-磷酸, 最终在G6PC水解作用下生成葡萄糖(图2).

3 糖异生调控机制

研究奶牛肝脏糖异生调控机制及营养调控至关重要. 到目前为止, 关于奶牛肝脏糖异生已取得一定的研究进展: 已清楚cAMP的效应元件结合蛋白(cAMP-response element binding protein, CREB)、叉头框转录因子1(forkhead transcription factor O1, FOXO1)、过氧化物酶体增殖激活受体-γ辅激活因子-1α(peroxisome proliferator-activated receptor γ coactivator 1-alpha, PGC-1α)、肝细胞核因子4α(hepatic nuclear factor 4 alpha, HNF4α)等重要转录因子与肝脏糖异生密切相关; 同时, 糖异生底物、关键酶和营养物质等在反刍动物肝脏糖异生过程中也发挥着重要的调控作用.

3.1 转录因子调节

反刍动物的主要糖异生底物为丙酸, 而非反刍动物则以乳酸、甘油及氨基酸为主. 此外, 反刍动物的胰岛素水平持续偏低, 这导致相关转录因子的调控呈现出物种特异性.

3.1.1 CREB

胰高血糖素结合肝细胞上的胰高血糖素受体(glucagon receptor, GCGR)并迅速激活环化腺核苷一磷酸(cyclic adenosine mono phosphate, cAMP)信号, 随后激活蛋白激酶A(protein kinase A, PKA), 使CREB的133位丝氨酸磷酸化, 从而乙酰化组蛋白H3和H4, 导致糖异生基因的转录激活[42,43]. 与之相反, 高浓度的胰岛素通过抑制cAMP信号抑制肝脏糖异生[44]. 同时, CREB调节转录辅激活因子2(CREB regulated transcription coactivator 2, CRTC2)转位到细胞核与CREB结合, 并进一步增强CREB介导的*PCK*和*G6PC*的基因转录[45~47]. 有研究表明, 腺苷酸活化蛋白激酶(AMP activated protein kinase, AMPK)可以磷酸化CRTC2, 使其停滞在细胞质内, 降低CREB的转录活性, 从而抑制肝脏糖异生[48~52]. 在非反刍动物中, CREB介导的糖异生活性主要受空腹与餐后血糖波动调控. 相比之下, 反刍动物血糖相对稳定、门静脉胰岛素浓度长期处于低水平, 使CREB在昼夜周期内均保持较高的磷酸化活性, 从而维持糖异生基因的稳定转录. 因此, cAMP-PKA-CREB/CRTC2轴参与反刍动物肝脏糖异生的转录调控, 其中CREB是该信号轴中的关键转录因子(图3).

3.1.2 PGC-1α

研究表明, PGC-1α能够结合糖异生基因*PCK1*和*G6PC*的启动子, 并促进这两个基因的表达[53,54], 而*PGC-1α*的表达受到CREB调控[55]. 哺乳动物雷帕霉素靶蛋白(mechanistic target of rapamycin, mTOR)是调控PGC-1α定位及活性的关键通路[56], 研究发现mTOR通路以PGC-1α依赖的方式调控糖异生[57]. 此外, 奶牛原代肝脏细胞实验发现, mTOR通路能够促进糖异生基因的表达, 包括编码催化丙酸转化为丙酮酸的酶类(*ACSS1*, *PCCA*, *MCEE*, *MMUT*及*SUCLG2*等), 及催化丙酮酸转化为葡萄糖的酶类(*PCK*及*FBP*等)[57], 揭示了mTORC1在奶牛肝脏糖异生中的重要作用(图3). 由于糖异生底物的差异, 反刍动物肝脏中PGC−1α更偏向促进丙酸代谢与线粒体氧化途径的耦合, 强化以丙酸为底物的糖异生. 而非反刍动物的PGC−1α主要参与乳酸与脂肪酸氧化供能的调节. 总体而言, 反刍动物PGC−1α在糖异生调控中的作用更持久.

3.1.3 FOXO1

FOXO家族转录因子参与糖异生基因的转录调控, 在非反刍动物中主要受胰岛素信号调节[58]. 研究表明, 肝脏*FOXO1*的敲除小鼠糖异生能力显著减弱, 而*FOXO1*的过表达降低了胰岛素对糖异生的抑制作用[59]. FOXO1蛋白与转录激活因子PGC-1α共同促进*PCK1*和*G6PC*的表达[60,61]. 研究证明, 胰岛素信号通过蛋白激酶B(protein kinase B, AKT)-FOXO1抑制糖异生[62,63]. 非磷酸化的FOXO1定位于细胞核, 而胰岛素信号激活AKT后磷酸化FOXO1使其进入到细胞质中, 进而抑制肝脏糖异生[64]. 此外, AMPK影响HNF4α及FOXO1的转录活性, 从而控制糖异生反应[65]. 与非

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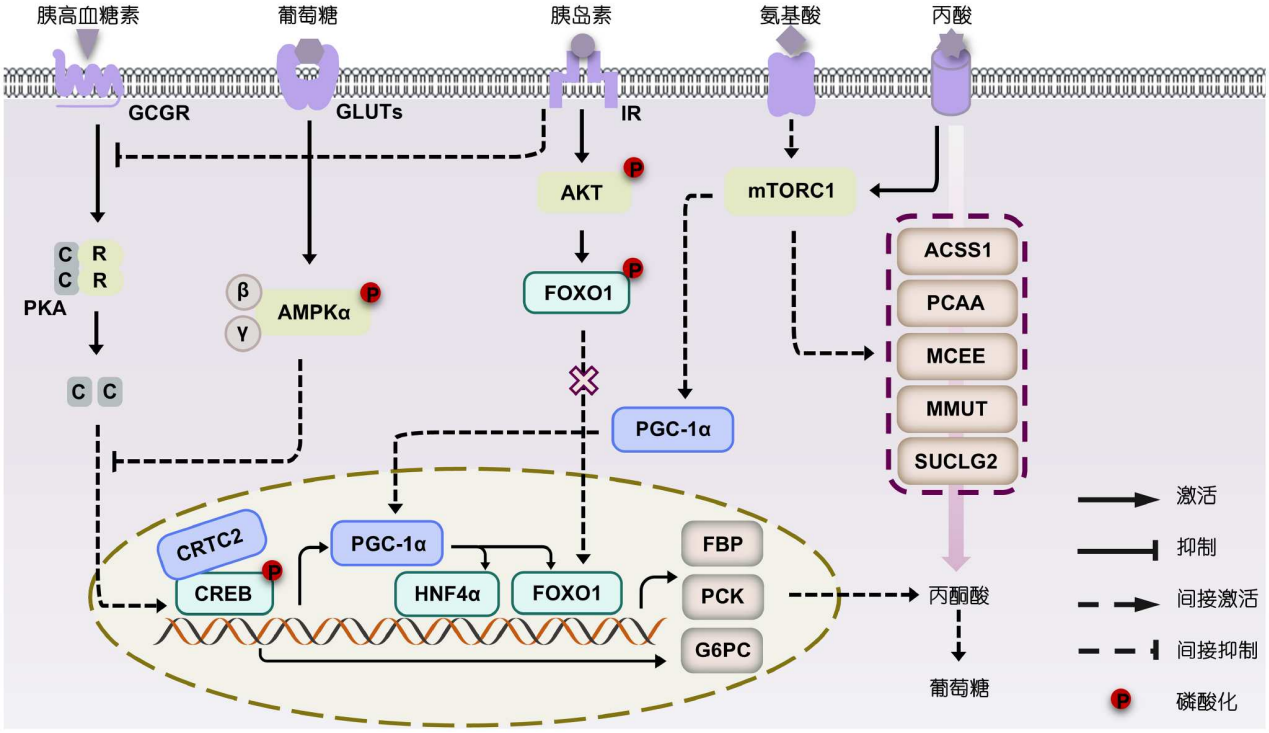


图 3 调控糖异生的转录因子
Figure 3 Transcription factors involved in gluconeogenesis regulation

反刍动物相比，反刍动物由于门静脉胰岛素浓度普遍偏低，FOXO1长时间位于核中，这使得糖异生基因持续表达，进而满足泌乳期间对葡萄糖的大量需求(图3).

3.2 糖异生底物调节

3.2.1 丙酸

丙酸作为瘤胃发酵的产物，是反刍动物肝脏糖异生的首要前体，其供给水平与葡萄糖生成量及代谢效率均呈显著正相关[66~68]. 研究证实，直接向山羊和奶牛瘤胃中灌注丙酸能增强肝脏糖异生，提升血糖[66,69]. 此外，丙酸还能在体外上调肝细胞中糖异生关键基因(*PCK*, *G6PC*)及转录因子*PGC-1α*的表达，进而促进糖异生，且其作用受mTOR通路调控[37,70~72]. 值得注意的是，以丙酸为底物的糖异生过程对短期胰高血糖素抑制不敏感，显示出其独特的生理调控特性[73]. 基于上述机制，调控日粮以增加丙酸产量成为改善反刍动物能量状态的有效手段. 例如，采用高淀粉日粮，或在饲料中添加莫能菌素、丙二醇等添加剂，均能有效提高瘤胃丙酸浓度，从而缓解围产期奶牛的能量负平衡[74~79]. 然而，丙酸的促糖异生效应并非线性，高浓度丙酸可能因耗竭三羧酸循环(tricarboxylic acid cycle, TCA)底物或通过代谢产物产生负反馈[80~82]. 综上所述，单纯追求丙酸产量最大化的饲养策略并非最优方案. 为确保TCA循环的稳健运行与整体糖异生效率，必须平衡丙酸与其他生糖前体(如生糖氨基酸)的供给. 这不仅为优化反刍动物营养策略提供了新思路，也为补充生糖氨基酸等功能性添加剂的应用奠定了理论基础(图4).

3.2.2 氨基酸

氨基酸(除赖氨酸和亮氨酸外)是肝脏糖异生的关键底物[83]. 高蛋白日粮可通过上调*G6PC*的表达进而增强肝脏的糖异生通量[84]. 特定氨基酸的补充也可调控糖异生，例如，蛋氨酸和亮氨酸可促进犊牛肝脏糖异生和血糖水平[85,86](图4).

3.2.3 游离脂肪酸与甘油

围产期奶牛的能量负平衡状态导致体脂动员，血浆中游离脂肪酸(nonestesterified fatty acid, NEFA)和甘油浓度升高[87]. 甘油不仅作为直接底物，还能通过

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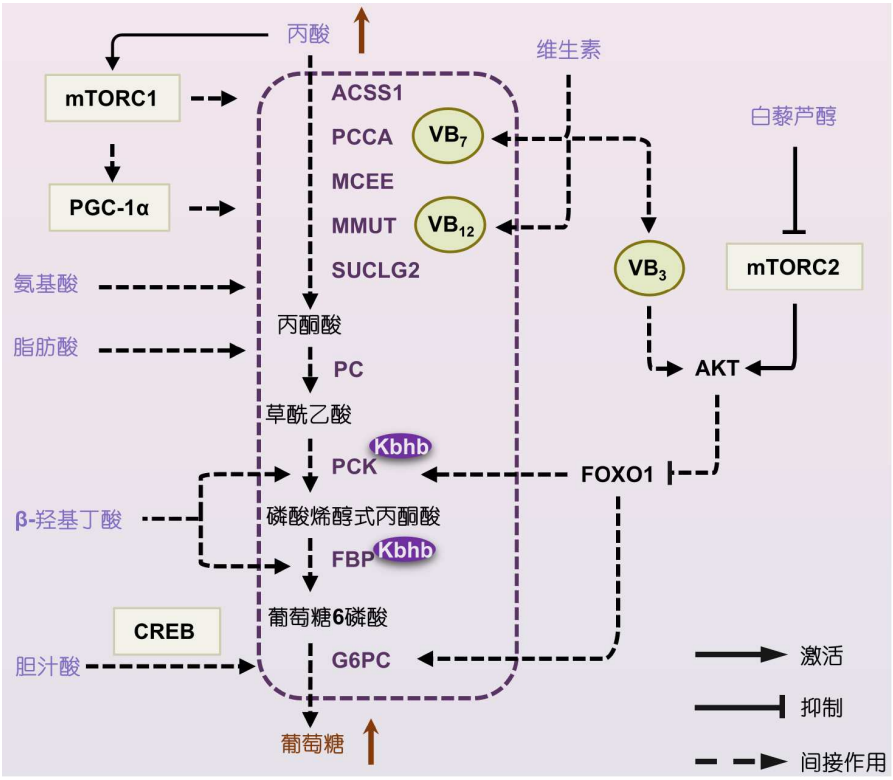


图 4　调控糖异生的营养物质
Figure 4　Nutrients involved in gluconeogenesis regulation

上调*PCK1*的表达来增强糖异生[88,89]. 同时, NEFA氧化生成的乙酰辅酶A可作为丙酮酸羧化酶(pyruvate carboxylase, PC)的别构激活剂, 并抑制丙酮酸脱氢酶复合体(pyruvate dehydrogenase complex, PDH)活性, 从而将代谢流导向糖异生途径[90~92]. 此外, β-羟基丁酸作为主要酮体, 可通过一种新型的翻译后修饰——β-羟基丁酰化(β-hydroxybutyrylation, Kbhb)——修饰糖异生关键酶FBP1和PCK1, 从而显著增强其催化活性与葡萄糖生成能力[93](图4). 这一研究结果提示, 适度水平的β−羟基丁酸不仅作为能量底物, 还可能充当信号分子, 通过调控Kbhb修饰影响肝脏糖异生关键基因的表达.

3.2.4　其他调节物质

多种微量营养素及生物活性物质也能调控肝脏糖异生. 在丙酸转变为琥珀酰辅酶A的过程中, 维生素B_7 (vitamin B_7, VB_7)是PCCA的辅酶, 而VB_{12}是MMUT的辅酶, 二者对利用丙酸进行糖异生至关作用[94~99]. 烟酸(VB_3)则可激活AKT-FOXO1信号通路, 调控*G6PC*和*PCK1*的表达以促进奶牛糖异生[100]. 白藜芦醇被证明能通过激活核因子(红细胞衍生2)相关因子2(nuclear factor erythroid 2-related factor 2, NRF2)通路缓解氧化应激, 并经由mTORC2-AKT通路增强奶牛肝脏细胞的糖异生能力[101]. 此外, 特定胆汁酸(牛磺脱氧胆酸、牛磺胆酸和甘胆酸)可作为信号分子, 通过激活其受体G蛋白偶联胆汁酸受体1(G protein-coupled bile acid receptor 1, TGR5), 引发cAMP-CREB信号级联反应, 进而上调糖异生关键基因(*FBP1*, *PCK1*和*G6PC*)的表达, 促进葡萄糖生成[102](图4).

综上所述, 这些内源性代谢物和外源性生物活性物质通过提供底物、调控关键酶的表达与活性以及激活特定信号通路等多种机制, 共同调节肝脏糖异生. 这提示它们可作为潜在的饲料添加剂, 用于促进奶牛肝脏糖异生效率与生产性能.

4　总结与展望

肝脏糖异生是维持奶牛能量稳态的核心生理过

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程, 能够满足其在泌乳期巨大的能量需求. 本综述系统梳理了奶牛肝脏糖异生的结构基础和基本生化过程, 并重点阐述了关键限速酶的转录调控网络及营养因素的多维度调控. 研究明确指出, 源自瘤胃发酵的丙酸是反刍动物糖异生的主要碳源前体. 尽管当前在分子机制及营养调控方面的研究已取得显著进展, 但仍存在若干亟待深入探索的前沿领域, 这些领域也预示着广阔的理论与应用前景.

在细胞异质性与器官互作层面, 未来的研究方向可归纳为以下两点. 首先, 尽管单细胞测序技术已成功构建了奶牛肝脏的转录组图谱, 并将肝实质细胞注释为沿中央静脉-门静脉轴呈功能梯度分布的十个亚型(HPE0~9), 揭示了肝脏功能的空间分区, 这与人和小鼠的肝脏结构和功能分区高度一致[103~105]. 然而, 一个关键的科学问题悬而未决: 在这些功能异质的细胞亚群中, 究竟是哪一群体更高效地负责以丙酸为主要底物的糖异生过程? 这一问题的解答对于深入理解肝脏糖异生的精细调控至关重要. 其次, 糖异生并非肝脏的独立功能, 肾脏、肠道乃至瘤胃上皮等多个组织均被证实具备糖异生能力. 然而, 不同哺乳动物中这些组织糖异生活性的相对贡献、组织偏好性及其生理意义尚未被完全阐明. 未来的研究需将视野从单一器官扩展至多器官系统, 重点解析肝脏与其他器官之间在信号分子、激素分泌及营养物质转运等方面的复杂通讯网络, 及其协同调控全身糖异生稳态的整合机制.

在研究手段与模型层面, 一个显著的技术瓶颈在于体外模型的缺乏. 哺乳动物肝脏在出生后经历一个快速生长与增殖阶段, 随后肝实质细胞增殖能力下降, 进入静息状态并逐渐形成多倍体. 多倍体化虽然是肝脏成熟的标志, 但也显著降低了细胞的增殖潜能和损伤修复能力[106]. 这一生物学特性导致从成年奶牛肝脏分离的原代肝细胞难以在体外扩增, 加之其对流式分选等操作的敏感性, 使得功能性细胞的获取与长期培养极为困难. 因此, 开发新型的、能够模拟体内生理状态的肝脏细胞培养体系或类器官模型, 是攻克这一技术壁垒、推动功能研究深入开展的迫切需求.

在精准调控与应用前景层面, 未来的研究应聚焦于反刍动物的生理特异性. 尽管糖异生通路在哺乳动物中具有保守性, 但奶牛独特的瘤胃发酵代谢模式必然决定了其调控机制的特殊性. 因此, 鉴定并功能验证奶牛特有的转录因子、辅因子及信号通路中的关键节点, 是揭示其糖异生调控网络全貌的核心任务. 为实现这一目标, 应整合运用多组学技术(如基因组学、转录组学、蛋白质组学、代谢组学和翻译后修饰组学), 对大规模生理及代谢数据进行系统性分析. 同时, 开展更多设计严谨的营养干预试验, 阐明不同营养物质对糖异生通量的精确影响, 从而为优化饲料配方、实现对奶牛肝脏糖异生的精准调控提供坚实的科学依据.

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Research progress on the regulatory mechanisms of gluconeogenesis in the liver of dairy cows

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Glucose serves as the core energy substrate driving milk synthesis and the fundamental structural unit for lactose synthesis, with its supply level directly determining the efficiency of milk production in dairy cows. However, the unique rumen microbial fermentation characteristics of dairy cows result in a significant portion of dietary glucose being converted into volatile fatty acids. Consequently, more than 80% of glucose in the body relies on hepatic gluconeogenesis. Therefore, it is crucial to deeply understand the regulatory mechanisms of hepatic gluconeogenesis in dairy cows to ensure their healthy and efficient production. This review systematically examines hepatic gluconeogenesis in dairy cows. First, it clarifies that the portal vein zone and central vein zone constitute the primary cellular compartments executing gluconeogenic functions based on liver structure and functional zonation. Second, it explores substrate preferences in hepatic gluconeogenesis, demonstrating that propionic acid serves as the predominant carbon source for gluconeogenesis in adult dairy cow livers, contributing 60%–74% of total carbon input. Furthermore, it provides a detailed overview of gluconeogenesis regulatory elements, mapping a coordinated regulatory network involving multiple transcription factors such as cAMP-response element binding protein (CREB), forkhead transcription factor O1 (FOXO1), peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC-1α), and hepatic nuclear factor 4 alpha (HNF4α). Finally, the present review outlines future research directions based on the current studies, aiming to provide theoretical foundations and technical support for improving glucose metabolism and enhancing production efficiency in dairy cows.

dairy cow, hepatic gluconeogenesis, regulatory mechanism, production efficiency

doi: 10.1360/SSV-2025-0380



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