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围产期奶牛脂肪肝发病机制研究进展

郭延生 毛永霞 王菲菲 李晨雷

(宁夏大学 动物科技学院, 银川 750021)

摘要 围产期奶牛脂肪肝作为一种高发的代谢性疾病, 不仅导致生产性能与繁殖能力下降, 还显著增加酮病、皱胃移位及乳腺炎等围产期疾病的风险, 严重制约我国奶牛养殖业的高质量可持续发展。本文系统综述了围产期奶牛脂肪肝的分型、临床表现、预防和治疗措施, 深入剖析围产期代谢变化、营养、表观遗传调控等多重诱因对脂肪肝发生与发展的作用, 并重点探讨了腺苷酸活化蛋白激酶(AMPK)、核转录因子NF-E2相关因子2(Nrf2)、内质网应激(ERS)、胰岛素抵抗等途径在该病中的分子机制。基于此, 本综述指出当前奶牛脂肪肝分子机制研究的不足, 强调深入挖掘其潜在生物标志物和精确治疗靶点, 将为厘清关键病理过程、优化诊断与防控策略提供重要科学依据。

关键词 脂肪肝; 围产期奶牛; 致病因素; 发病机制

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Research progress on the pathogenesis of fatty liver in perinatal dairy cows

GUO Yansheng, MAO Yongxia, WANG Feifei, LI Chenlei

(College of Animal Science and Technology, Ningxia University, Yinchuan 750021, China)

Abstract Perinatal fatty liver in dairy cows, a prevalent metabolic disorder, not only causes a decline in production performance and reproductive capacity but also significantly increases the risk of perinatal diseases (e.g., ketosis, abomasal displacement, and mastitis). This condition seriously restricts the high-quality and sustainable development of the dairy cattle industry in China. This article systematically reviews the classification, clinical symptoms, prevention and therapeutic strategies for periparturient fatty liver disease in dairy cattle. It deeply analyzes the multiple influencing factors such as metabolic changes, nutrition, and epigenetic regulation during the perinatal period on the occurrence and development of fatty liver, and focuses on discussing the molecular mechanisms of adenylyate activated protein kinase (AMPK), nuclear transcription factor NF-E2-related factor 2 (Nrf2), endoplasmic reticulum stress, and insulin resistance in this disease. Building on the analysis, the article further identifies limitations in current research on the molecular mechanisms of dairy cow fatty liver. It emphasizes the need to investigate potential biomarkers and precise therapeutic targets in depth, which will provide a robust scientific foundation for elucidating key pathological processes and optimizing diagnostic tools and prevention strategies.

Keywords fatty liver; perinatal dairy cows; causative factors; pathogenesis

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第一作者: 郭延生 (ORCID: 0000-0002-9882-0706), 教授, 主要从事反刍动物常见病发病机制解析和中兽药及天然小分子药物的研发与创制研究, E-mail: guoyansheng1978@163.com

近年来,消费者对优质奶产品需求的持续增长推动了育种技术与营养管理体系的迭代升级,显著提升了全球牛奶产量^[1]。然而,高产奶量加剧了奶牛的代谢负荷,尤其是在围产期(产前3周至产后3周)。在此期间,奶牛在短时间内经历从妊娠至泌乳的剧烈代谢转换。这一过程伴随着能量负平衡(Negative energy balance, NEB)和内分泌紊乱,使其对营养代谢性疾病尤为敏感。流行病学调查显示,约50%的经产奶牛产后1个月内出现肝脏甘油三酯(Triglyceride, TG)异常蓄积,其中约30%的奶牛发展为脂肪肝或脂肪肝综合征^[2]。肝脏中TG的过量沉积不仅损伤肝功能(如抑制糖异生与极低密度脂蛋白(Very low density lipoprotein, VLDL)合成),还会诱发胰岛素抵抗、炎症与氧化应激^[3]。同时,脂肪肝会导致产奶量骤降和繁殖性能障碍,以及增加胎衣不下、子宫内膜炎、皱胃移位与产后瘫痪等并发症的风险。这些连锁反应最终严重损害奶牛的生产性能、使用年限及牧场的经济效益。

过去几十年,围产期奶牛脂肪肝的相关研究已从病理描述拓展至分子机制层面。研究不仅初步揭示了能量负平衡触发脂肪动员导致肝脏脂质蓄积的关联,还揭示了多条关键信号通路在奶牛脂肪肝中的调控作用。例如,Du等^[4]研究发现,中度脂肪肝奶牛肝脏中p-AMPK和p-ACC1的蛋白质表达水平下调,表明腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)信号通路受到抑制。Gao等^[5]研究通过转录组学分析证实,围产期奶牛主要通过过氧化物酶体增殖物激活受体(Peroxisome proliferator-activated receptor, PPAR)启动肝脏代谢,应对围产后期的代谢应激。Gao等^[6]研究发现,生长激素可通过激活细胞外信号调节激酶(Extracellular signal-regulated kinases, ERK)/激素敏感脂肪酶(Hormone-sensitive triglyceride lipase, HSL)信号通路,加剧围产期奶牛过度脂肪动员并降低其胰岛素敏感性。然而,现有研究成果比较碎片化,对奶牛脂肪肝发病机制的系统性认识尚不完善。因此,本文系统阐述了围产期奶牛脂肪肝的分型、临床表现、致病因素、分子机制及其预防和治疗措施,以期后续的机理探索、风险评估与干预策略优化提供理论依据。

1 围产期奶牛脂肪肝的分型

奶牛肝脏中TG的合成速率超过分解代谢水平

时,将导致TG在肝细胞内的异常蓄积,继而诱发脂肪性肝病或脂肪肝综合征。奶牛脂肪肝临床诊断可通过肝穿刺活检、经典Ried方程或影像学检查进行确诊。其中肝组织TG含量作为关键诊断指标,其病理学分级标准表明:正常奶牛肝脏TG含量低于1%;1%~5%判定为轻度脂肪肝;5%~10%判定为中度脂肪肝;超过10%则判定为重度脂肪肝^[7]。据Bobe等^[8]调查指出,泌乳初期4周内奶牛重度脂肪肝发病率达5%~10%,中度脂肪肝发病率更高达30%~40%。为替代创伤性肝穿刺活检,研究者相继开发了多种无创或微创的诊断方案。经典Ried方程将多项代谢参数整合为单一评分用于量化肝脂质沉积^[9]。

计算公式如下:

$$Y = -0.51 - 0.003a + 2.84b - 0.0528c \quad (1)$$

式中:Y为肝脏脂肪变性指数;a为非酯化脂肪酸(NEFA)含量,mmol/L;b为葡萄糖(GLU)含量,mmol/L;c为天门冬氨酸氨基转移酶(AST)含量,U/L。

当 $Y > 1$ 时为正常,当 $0 < Y < 1$ 时为中度脂肪肝,当 $Y < 0$ 时为重度脂肪肝^[10]。血清非酯化脂肪酸(Nonesterified fatty acid, NEFA)、葡萄糖(Glucose, GLU)和 β -羟基丁酸(β -hydroxybutyrate, BHBA)等可评估脂质动员水平,天门冬氨酸氨基转移酶(Aspartate aminotransferase, AST)、丙氨酸氨基转移酶(Alanine aminotransferase, ALT)和谷氨酸脱氢酶(Glutamate dehydrogenase, GDH)等则反映肝细胞损伤,多指标联合可显著提高间接诊断的准确性。影像学方面,B超可通过测定肝实质回声及肠系膜(周血管)脂肪厚度预测围产期高产奶牛的脂肪肝风险,脂肪肝的判定临界值为肝脏深度(Depth of the liver, DL) ≥ 152.6 mm、内脏周围脂肪深度(Depth of perivisceral adipose tissue, DPAT) ≥ 175.2 mm和内脏周围脂肪厚度(Thickness of perivisceral adipose tissue, TPAT) ≥ 21.5 mm^[11]。由于设备便携、操作简便,该方法适合在牧场现场进行快速筛查推广。然而,环境、胎次和饲养模式差异会显著影响阈值设定,限制了这些方法的普适性。因此,虽然经典Ried方程和影像学检查技术避免了活体检查,但其通用性和灵敏度仍需进一步验证与优化。总体而言,现行监测高度依赖血液学指标和肝穿刺活检,仍缺乏灵敏、无创且可在牧场现

场快速应用的早期预警技术,难以及时锁定高风险个体。参考相关文献,本文还对临床上健康奶牛和脂肪肝奶牛的肝脏病理变化、采食量、产奶量以及繁殖性能进行了归纳(表1)。

表1 健康奶牛与脂肪肝奶牛的分类信息
Table 1 Classification information of healthy cows and cows with fatty liver

项目 Project type	健康奶牛 Healthy dairy cows	脂肪肝奶牛 Fatty liver dairy cows	参考文献 References
肝脏病理变化 Liver pathological changes	肝脏形态正常,无明显TG浸润	轻度: TG在肝小叶附近浸润 中度: TG在整个肝脏浸润 重度: 肝脏肿大坏死	Bobe等 ^[12]
干物质采食量/(kg/d) Dry matter intake	19.6	轻度: 19; 中度: 18.6	Zhang等 ^[13]
	22.0±0.3	轻度: 21.5±0.319; 中度: 21.1±0.319	Arshad等 ^[14]
	21.1	轻度和中度: 19.6	Dong等 ^[15]
产奶量/(kg/d) Milk yield	35.5	轻度: 33.5; 中度: 30.8	Zhang等 ^[16]
	36.13	中度: 34.65	Wang等 ^[17]
	31.8	轻度和中度: 29.1	Dong等 ^[18]
繁殖相关疾病发病率/% Incidence of reproduction-related diseases	胎衣不下、产褥期子宫炎和子宫炎的发病率分别为(9.3±2.7)%、(6.9±2.3)%和(12.5±3.4)%; 首次受胎率(39.4±4.5)%	轻度: 胎衣不下、产褥期子宫炎和子宫炎的发病率分别为(11.9±3.2)%、(10.2±3.4)%和(18.2±4.5)%; 首次受胎率(35.8±4.1)% 中度: 胎衣不下、产褥期子宫炎和子宫炎的发病率分别为(15.1±4.7)%、(14.7±6.0)%和(25.7±6.8)%; 首次受胎率(32.5±5.1)%	Higgins等 ^[19] Arshad等 ^[20]
		轻度和中度: 子宫内膜炎发病率16.9%	Jorritsma等 ^[21]

2 围产期奶牛脂肪肝的临床表现及危害

奶牛轻中度脂肪肝通常在4周左右可自发缓解,但由此引发的泌乳性能衰退往往难以恢复至正常水平,同时伴有免疫抑制和繁殖障碍等负面影响。重度脂肪肝奶牛则表现为精神萎靡、食欲废绝及间歇性腹痛等临床症状,甚至可能引发严重衰弱和内毒素血症等并发症,最终导致病牛死亡。奶牛脂肪肝引起的代谢稳态失衡、炎症反应、氧化应激以及肝功能损伤会直接损害机体功能,尤其表现为免疫系统的抑制,包括免疫功能低下、子宫免疫应答时间延长及强度减弱等^[22]。这些病理变化增加了奶牛对其他疾病的易感性。具体而言,由代谢紊乱和炎症反应导致的胃肠蠕动抑制,会提高皱胃移位的发生风险^[23]。肝脏脂质积累及其伴随的炎症反应与氧化应激环境,会加重乳腺炎和子宫内膜炎的发展^[24]。而免疫功能的抑制不仅增加乳腺对病原体的易感性并延缓乳腺组织的修复,还会导致子宫复旧障碍和繁殖力下降^[25]。上述健康问题给奶

牛养殖业带来了巨大经济损失。脂肪肝相关疾病会导致治疗成本增加、产犊间隔延长及母牛平均寿命缩短。据统计,我国每年在治疗奶牛脂肪肝上的经济支出约为3 000万美元^[26],且奶牛在泌乳期3个月内的平均淘汰率约为27%^[27]。因此,脂肪肝不仅损害奶牛机体健康,还大幅增加了牧场医疗支出,成为制约奶牛业可持续发展的关键问题。

3 围产期奶牛脂肪肝的致病因素

3.1 围产期奶牛代谢变化

随着胎儿快速生长与子宫扩张,妊娠后期奶牛胃肠道(尤其是瘤胃)受到挤压,导致其物理容积受限且蠕动功能减弱,直接引发采食量下降^[28]。采食量下降会减弱瘤胃发酵活动,进一步抑制奶牛的食欲。与此同时,围产期奶牛体内激素水平发生剧烈变化,如孕酮^[29]、皮质醇^[30]、生长激素及瘦素^[31]等。瘦素是一种由脂肪细胞分泌的肽类激素,不仅能抑制奶牛的自愿采食,还能导致围产期奶牛外周胰岛素抵抗^[32]。这些激素的动态变化会影响奶牛的食

欲控制中枢,产生强烈的食欲抑制效应^[33]。因此,围产期奶牛因采食量降低及胎儿生长和泌乳启动能量激增,最终陷入NEB状态^[34]。在反刍动物能量代谢体系中,肝糖异生作为血糖稳态的核心调控节点,大部分GLU由丙酸等前体转化而成。然而,当血液中NEFA与BHBA浓度过高时会强烈抑制生长激素调控的肝糖异生并破坏GLU的稳态平衡^[35]。同时,奶牛在产后对GLU的需求增加,而泌乳早期的胰岛素水平往往会下降^[36],这一变化会进一步刺激脂肪组织分解,释放更多NEFA,形成恶性循环。此外,NEB引起的脂肪动员会增加活性氧(Reactive oxygen species, ROS)的产生,当产生的ROS超出机体抗氧化系统的清除能力,则会引发脂质过氧化^[37]。NEB状态还会降低奶牛免疫系统的敏感性,导致免疫抑制^[38]。在此状态下,不佳的卫生条件会显著提升产后奶牛感染细菌或病毒的风险,进一步加重机体代谢负荷。此外,若饲养环境存在空间局促、通风不畅、温湿度失衡,且缺乏充足户外活动区域与规律运动条件,奶牛机体将应激并分泌儿茶酚胺类物质,驱动脂肪组织分解,致使脂质在肝脏异常沉积,最终引发脂肪肝病变^[39]。

3.2 营养因素

碳水化合物约占围产期奶牛日粮的70%,是主要的能量来源^[40]。当日粮中缺乏碳水化合物(如淀粉)时,会抑制瘤胃发酵,减少挥发性脂肪酸(Volatile fatty acid, VFA)的生成。作为关键VFA之一的丙酸,不仅是糖异生的重要底物,为奶牛提供40%~70%的GLU,还具有抑制炎症反应、提高机体免疫力的功能^[41]。研究发现,日粮中添加丙酸钠能有效减少围产后期奶牛的脂肪动员,缓解NEB状态^[42]。为满足奶牛围产期的营养需求,牧场常采用高精料日粮来饲喂围产期奶牛。这类日粮虽能满足营养需求,但会加速瘤胃发酵产生大量VFA,导致瘤胃pH值下降。由此形成的酸性环境会促使脂多糖(Lipopolysaccharide, LPS)等代谢产物在瘤胃中大量生成,随后经瘤胃上皮吸收入血并抵达肝脏。LPS不仅能刺激炎性因子表达,造成肝细胞炎性损伤与肝功能衰退,还能结合脂蛋白向肝脏转运,促进肝内TG蓄积^[43]。已有研究证实,奶牛饲喂高精料日粮会导致肝脏纤维化、脂质积累以及炎症反应^[44-45]。因此,围产期奶牛日粮中可发酵淀粉的添加量需严格把控,以平衡营养供应与瘤胃健康。

甲基供体(如胆碱和蛋氨酸)的缺乏会导致围产期奶牛的营养和能量摄入不足,加重NEB状态。其中,作为机体必需营养素,胆碱不仅能增加奶牛的采食量,还能促进乳蛋白合成,进而提高奶产量和乳脂率。而蛋氨酸作为反刍动物合成蛋白质的必需氨基酸,可直接参与机体氨基酸代谢,对消化功能和生长性能产生重要影响^[46-47]。研究发现,日粮中添加过瘤胃胆碱和蛋氨酸铬能够增加围产期奶牛采食量,改善能量需求,调节糖脂代谢,改善奶牛NEB状态^[48]。因此,日粮中适当添加胆碱、蛋氨酸等营养素有助于应对围产期奶牛面对的营养挑战。此外,微量元素在奶牛多种生理过程中发挥重要作用,尤其是影响能量代谢和免疫功能。例如,日粮中缺乏钙会抑制糖异生过程^[49];钾、镁和钙的缺乏则会抑制采食量并减少瘤胃蠕动,从而加剧奶牛NEB状态^[50];硒的摄入会影响奶牛脂质代谢并提高围产期奶牛的免疫力^[51]。因此,在日粮中科学补充微量元素对于预防围产期奶牛脂肪肝具有重要作用。

3.3 表观遗传因素

表观遗传调控网络作为基因表达的调节系统,通过DNA甲基化、非编码RNA分子等调控机制影响动物的生长发育、繁殖功能及疾病易感性^[52]。其中,DNA甲基化对维持基因组稳定性及调控基因表达具有重要作用。在真核生物中,这一过程由DNA甲基转移酶(DNA methyltransferases, DNMT)催化完成,在CpG岛(胞嘧啶-磷酸-鸟苷)胞嘧啶上添加甲基基团。由于CpG岛通常位于基因启动子区域,其甲基化修饰可通过基因转录沉默抑制基因的表达^[53]。该修饰过程受多因素影响,包括RNA干扰、DNMT活性异常、组蛋白甲基化、环境温度波动及营养供给状态等^[54]。表观基因组分析发现,牛体细胞中DNA甲基化动态与生长发育、生产性状密切相关^[55]。在代谢性疾病领域,Murphy等^[56]研究发现,非酒精性脂肪性肝病(Nonalcoholic fatty liver disease, NAFLD)晚期患者肝脏中组织修复基因发生去甲基化和高表达,1-碳代谢途径相关基因则发生高甲基化和低表达。1-碳代谢途径受破坏后会加剧肝细胞脂肪变性进程^[57]。该研究证明了检测特定基因的甲基化水平可用于NAFLD的早晚期判定。未来研究可以借鉴这一思路深入探究奶牛脂肪肝发生发展中是否存在类似的甲基化水平变化,

从而为奶牛脂肪肝的诊断开辟新的途径。

在非编码RNA分子方面,miRNA作为长度19~25核苷酸的小RNA,虽无编码蛋白质功能,但可参与细胞周期进程、免疫应答调控及脂质代谢稳态等多种生物过程。其表达受代谢物、激素、细胞因子和营养物质等影响^[58]。在肝脏中,特异性miR-122被证实能够调控肝脏脂肪酸 β 氧化和胆固醇生物合成的速率^[59],这突出了miRNA在代谢调控中的核心作用。研究表明,miRNA表达紊乱与多种疾病进程密切相关,包括NAFLD、非酒精性脂肪肝炎(Non-alcoholic steatohepatitis, NASH)以及肝细胞癌(Hepatocellular carcinoma, HCC)等^[60]。这些发现扩充了研究者对miRNA在肝脏疾病中作用的理解。在反刍动物的研究中,Fatima等^[61]在奶牛肝脏的脂肪酸去饱和酶2(Fatty acid desaturase 2, *FADS2*) 3'UTR区域中鉴定出miR-140和miR-2885结合位点,而该酶在脂类生物合成中起限速作用,这表明miRNA在反刍动物的脂质代谢调控中可能具有特殊的重要性。Romao等^[62]的饮食干预研究提供了有力证据,证实miRNA可能参与牛脂肪生成的调控过程。进一步研究揭示了miR-17-92的过表达通过抑制关键细胞周期调节因子和肿瘤抑制因子Rb2/p130,促进前脂肪细胞分化并诱导

TG蓄积^[63]。因此,系统解析miRNA在奶牛脂质代谢调控网络中的分子作用机制,有望为奶牛脂肪肝的精准防治开辟创新性路径。

4 围产期奶牛脂肪肝的发病机制

奶牛脂肪肝主要发生于围产期,其发病机制与NEB状态下的代谢紊乱密切相关。围产期奶牛由于干物质采食量(Dry matter intake, DMI)显著降低与泌乳能量需求增加等因素的影响而发生能量摄入与消耗严重失衡。这种持续性的能量缺口促使机体启动脂肪动员机制,通过增强脂解作用释放出大量NEFA并被转运至肝脏代谢^[64]。NEFA主要通过以下途径进行代谢:1)完全氧化;2)不完全氧化;3)重新酯化生成TG,并以VLDL形式输出肝脏,并被外周组织利用。在完全氧化过程中,NEFA经线粒体 β 氧化转化为乙酰辅酶A并进入三羧酸循环,为机体提供能量。然而,围产期奶牛在经历NEB时,其肝脏的脂肪酸完全氧化能力和VLDL输出能力会降低。NEFA会通过不完全氧化生成乙酰辅酶A并进一步生成乙酰乙酸和BHBA等酮体,当BHBA浓度超过1.2 mmol/L时就会引起奶牛酮病^[65];而重新酯化生成的TG在肝脏内积累,则会诱发奶牛脂肪肝(图1)。

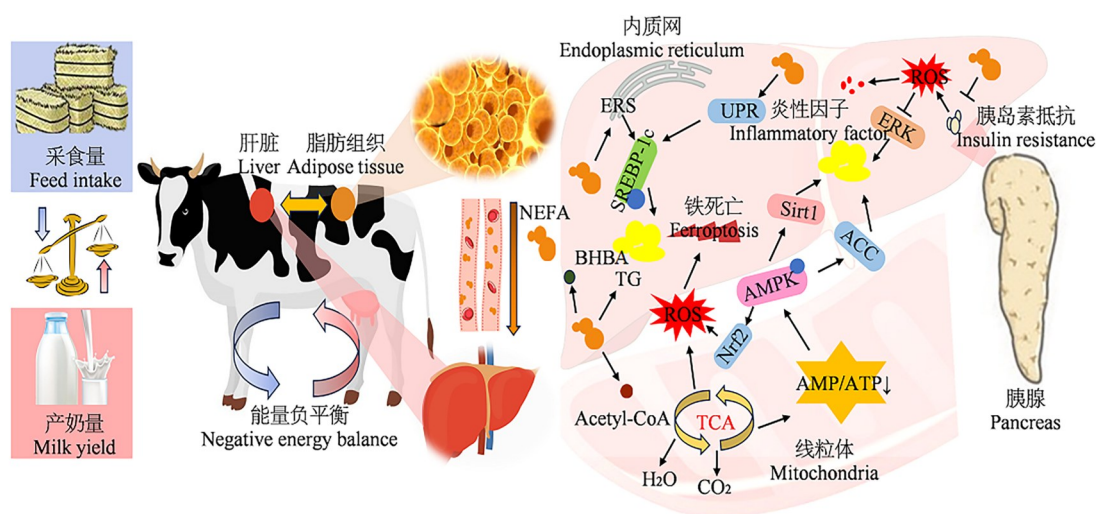


图1 围产期奶牛脂肪肝发病机制图

Fig. 1 Diagram of the pathogenesis of fatty liver in perinatal dairy cows

围产期奶牛下丘脑的食欲素-A/前阿片黑皮素原(Orexin-A/Pro-opiomelanocortin, OX-A/POMC)信号通路受到抑制会干扰正常进食行为,

进而引发NEB^[66]。AMPK是细胞内关键的能量感受器和代谢稳态调节器,在调控脂质代谢中发挥关键作用。肝激酶B1(Liver kinase B1, LKB1)作为

AMPK的上游激酶,在细胞能量应激时可从细胞核转位至细胞质,通过磷酸化激活AMPK^[67]。当细胞内AMP/ATP比值降低时,LKB1会抑制AMPK的磷酸化过程^[68],此抑制效应通过双重机制调控脂质代谢:一方面,AMPK磷酸化受阻会抑制乙酰辅酶A羧化酶(Acetyl-CoA carboxylase, ACC)的磷酸化,导致丙二酰辅酶A生成减少^[69]。由于丙二酰辅酶A是肉毒碱棕榈酰基转移酶1(Carnitine palmitoyltransferase 1, CPT1)的变构抑制剂,其含量下降会通过降低CPT1表达来抑制脂肪酸氧化^[70]。另一方面,该抑制作用会减弱沉默信息调节因子(Silent information regulator 1, SIRT1)活性并下调过氧化物酶体增生物激活受体 γ 共激活因子1 α (Peroxisome proliferator activated receptor gamma co-activator 1 α , PGC1 α)表达,进而增强脂肪酸合成酶(Fatty acid synthetase, FAS)、ACC等脂质合成相关基因表达,促进脂肪酸合成^[71]。在氧化应激调控中,AMPK磷酸化抑制会下调核转录因子NF-E2相关因子2(Nuclear factor erythroid 2-related factor 2, Nrf2)的表达^[72]。作为氧化应激的关键调控因子,Nrf2表达降低会导致磷酸酰胺腺嘌呤二核苷酸醌氧化还原酶(NQO)-1、超氧化物歧化酶2(Superoxide dismutase 2, SOD2)等抗氧化酶的合成减少,加剧细胞氧化损伤。成纤维细胞生长因子21(Fibroblast growth factor 21, FGF21)可以通过激活AMPK信号通路,下调甾醇调节元件结合转录因子1(Sterol regulatory element binding transcription factor 1, *SREBF1*)、乙酰辅酶A羧化酶 α (Acetyl-CoA carboxylase alpha, *ACACA*)和脂肪酸合成酶(Fatty acid synthase, *FASN*)等脂质合成基因的表达,从而发挥抑制脂质合成与增强脂肪代谢的作用^[73]。Cheng等^[74]研究发现, α -酮戊二酸能够通过激活AMPK-PGC-1 α /Nrf2通路来预防高脂血症诱导的肝脂质积累、线粒体功能障碍和氧化应激。因此,AMPK/ACC/CPT1轴与AMPK/Sirt1/PGC-1 α 轴共同构成脂质代谢的调控通路,而AMPK/Nrf2通路则主要参与氧化应激的调节,三者通过协同作用调控细胞内脂质稳态与氧化还原平衡。

肝细胞中过量NEFA积累可激活内质网应激传感器(PERK、IRE1 α 和ATF6)和上调激活转录因子4(Activating transcription factor 4, ATF4)等UPR下游基因,促进固醇调节元件结合转录因子1c

(Sterol regulatory element-binding transcription factor 1c, *SREBP-1c*)表达并上调*ACACA*和*FASN*等脂肪生成基因的表达,最终加剧奶牛肝细胞的脂质蓄积,增加高产奶牛的脂肪肝发生风险^[75]。同时,UPR的PERK和IRE1 α 分支还能通过内质网应激(Endoplasmic reticulum stress, ERS)介导胰岛素抵抗的发生^[76]。胰岛素抵抗是指靶器官或组织对胰岛素的敏感性与反应性降低。而奶牛由于泌乳期的高能量需求,常伴随外周胰岛素抵抗及胰岛素水平下降。在胰岛素抵抗状态下,胰岛素无法有效抑制肝GLU生成,但会刺激脂肪合成,进而引发高血糖症与高甘油三酯血症^[77]。胰岛素抵抗还会进一步加剧机体氧化应激与炎症反应。Li等^[78]研究表明*SREBP-1c*通过促进牛肝细胞内ROS生成来增强核因子 κ B(Nuclear factor κ B, NF- κ B)信号通路的过度激活,从而进一步加剧脂肪肝奶牛的肝脏炎症损伤。脂肪肝奶牛肿瘤坏死因子- α (Tumour necrosis factor- α , TNF- α)和白细胞介素-6(Interleukin 6, IL-6)等促炎细胞因子浓度升高^[79]。高浓度NEFA通过诱导ROS生成,激活JNK信号通路并抑制ERK信号通路,导致p53转录激活与Nrf2转录抑制,进而引发氧化应激性肝损伤,促进脂肪肝等疾病发生^[80-81]。此外,肝细胞内过量ROS可触发脂质过氧化反应,导致细胞发生铁死亡。铁死亡是一种铁离子依赖性的程序性细胞死亡,其核心机制是谷胱甘肽代谢异常引发的脂质过氧化级联反应^[82]。Tao等^[83]研究发现,肝脏铁蓄积通过激活c-Myc-ACSL4调控轴驱动铁死亡过程,进而加速脂肪肝的发展。

综上,奶牛NEB促使肝脏大量摄取NEFA。这不仅可以抑制AMPK的磷酸化(AMP/ATP比值降低时),还会激活ERS以及诱导胰岛素抵抗,共同导致肝细胞内脂质过度积累,最终引发脂肪肝。过量NEFA和脂质蓄积会引发ROS爆发,进而通过诱发氧化应激(抑制Nrf2)、炎症反应(激活NF- κ B)及铁死亡(激活c-Myc-ACSL4)等途径共同造成肝细胞损伤,最终加剧脂肪肝病理进程。

5 围产期奶牛脂肪肝的预防和治疗措施

营养调控是预防围产期奶牛脂肪肝的关键策略,通过精准管理DMI来优化日粮能量。研究表明适度提升日粮能量密度或增加饲喂频率(每天3~

4次)能有效缓解围产期奶牛的NEB,降低脂肪肝的发生率^[84-85]。此外,过瘤胃脂肪补充也是预防该病的关键措施之一,研究发现补充鱼油后奶牛血浆中NEFA和BHBA水平显著降低^[86]。一些特定的营养补充剂,如胆碱和丙二醇(Propylene glycol, PG),同样能预防脂肪肝。胆碱会增强肝脏VLDL的分泌,而PG则有助于减少脂肪酸的动员,从而改善奶牛的代谢状态^[87]。另有研究发现,通过补充PG与过瘤胃分支链氨基酸(Rumen protected branched chain amino acids, RP-BCAA)可有效降低奶牛肝脏TG水平,减少肝脏脂肪变性。在对比研究中,接受RP-BCAA和RP-BCAA加PG的奶牛在哺乳初期表现出较低的肝脏TG水平和较低的AST及GDH活性^[88]。外源胰岛素的应用同样显示出改善奶牛代谢状态的潜力。一项研究探讨了缓释胰岛素(Slow release insulin, SRI)对奶牛代谢参数的影响,结果表明,低剂量的SRI(0.14 IU/kg)能有效降低血浆NEFA和TG浓度,同时维持血浆GLU浓度、DMI和乳量的稳定^[89],提示外源胰岛素可辅助治疗围产期奶牛脂肪肝和酮病。

6 小结与展望

围产期奶牛脂肪肝是一种多因素、多通路介导所致的复杂代谢性疾病。其核心病理特征为NEB状态下肝脏脂质代谢失衡,同时伴随炎症反应、氧化应激和细胞凋亡的发生。目前研究已证实AMPK、Nrf2、ERS和胰岛素抵抗等通路在调控脂质代谢、氧化应激与炎症反应中发挥关键作用;同时,DNA甲基化与miRNA等表观遗传机制对基因的表达调控也日益受到关注。但目前对奶牛脂肪肝的分子调控机制尚未完全阐明,潜在生物标志物和精确治疗靶点仍有待挖掘。DNA甲基化和miRNA在围产期奶牛脂肪肝发生中的具体作用机制是未来研究方向之一;同时,可将基因组学、转录组学、蛋白质组学和代谢组学等多组学结果进行整合系统解析奶牛脂肪肝的分子调控网络,挖掘潜在的生物标志物和治疗靶点;此外,可进一步开发基于表观遗传调控与生物标志物的精准营养干预方案,从而实现更高效的生产管理和围产期奶牛脂肪肝的防治。

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第一作者简介: 郭延生, 博士, 教授, 博士生导师。中国畜牧兽医学会上兽医学分会理事, 主要从事反刍动物常见病发病机制解析和中兽药及天然小分子药物的研发与创制。近年来, 在研或完成国家自然科学基金地区项目3项、宁夏重点研发计划项目1项、宁夏自然科学基金项目3项, 宁夏回族自治区县域成果引进项目1项; 获宁夏回族自治区科技进步三等奖1项, 国家发明创业奖创新奖1项。以第一或通讯作者发表研究论文30余篇, 其中SCI收录10余篇; 参编教材1部, 著作2部, 鉴定省级科研成果1项。