

乳酸化在脓毒症相关器官损伤中的机制研究

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收稿日期: 2025年9月21日; 录用日期: 2025年10月14日; 发布日期: 2025年10月22日

摘要

脓毒症作为严重困扰人类健康的疾病, 具有致死率高, 预后差等特点。因脓毒症病理生理机制复杂, 并且易合并多脏器损伤, 目前仍缺乏可行的治疗方法来提高患者生存率, 因此, 了解脓毒症中器官损伤的潜在机制对于制定有效的治疗策略至关重要。研究表明, 乳酸化修饰通过调控免疫反应、炎症过程以及细胞信号通路等, 与脓毒症的严重程度和预后密切相关。本文就乳酸化在脓毒症诱导的相关脏器损伤中的研究作一综述, 旨在为脓毒症的治疗提供临床思路。

关键词

脓毒症, 乳酸化, 器官损伤

Study on the Mechanism of Lactylation in Organ Damage Related to Sepsis

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Received: September 21, 2025; accepted: October 14, 2025; published: October 22, 2025

Abstract

As a disease that seriously plagues human health, sepsis has the characteristics of high mortality and poor prognosis. Because the pathophysiological mechanism of sepsis is complex and prone to multiple organ damage, there is still a lack of feasible treatment methods to improve patient survival. Therefore, understanding the underlying mechanisms of organ damage in sepsis is crucial to formulating effective treatment strategies. Studies have shown that lactylation is closely related to the severity and prognosis of sepsis by regulating immune responses, inflammatory processes, and

cellular signaling pathways. This paper reviews the research on lactylation in related organ damage induced by sepsis, aiming to provide clinical ideas for the treatment of sepsis.

Keywords

Sepsis, Lactylation, Organ Damage

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1. 引言

全球每年新增脓毒症病例超过 4890 万例，死亡人数约为 1100 万例，占全球死亡人数的 20% [1]。经过数十年的研究，脓毒症的机制及其诊治仍然是难题，且大多基于稳定血流动力学、抗感染、维持器官功能等支持疗法，到目前为止尚无特定的诊断或治疗指标[2] [3]。近年来，脓毒症患者的能量代谢改变逐渐成为研究热点。赵等[4]研究发现了一种新型的酸化修饰——乳酸化修饰，并证明乳酸盐可以直接促进组蛋白乳酸化并调节蛋白质基因表达。这一发现揭示了乳酸水平与脓毒症病理生理学和免疫学之间的相关性，为脓毒症的后续研究开辟了新思路。

乳酸在脓毒症中既是代谢产物又是免疫调节分子，可通过代谢重编程、表观遗传修饰和信号通路调控影响炎症与免疫平衡。研究表明，乳酸可促进巨噬细胞的促炎反应，并通过增加活性氧生成驱动脓毒症早期的炎症反应[5]。而且，乳酸还可通过改变细胞表面蛋白表达和细胞因子分泌，影响抗原呈递和免疫应答[6]。乳酸化是一种由乳酸驱动的蛋白质翻译后修饰，主要发生在组蛋白和非组蛋白的赖氨酸残基上。这种修饰通过改变蛋白质功能参与免疫调节、炎症反应和细胞信号传导[7]-[9]。在脓毒症中，糖酵解增强导致乳酸积累，进而引起乳酸化修饰水平升高，与疾病严重程度和预后密切相关[9] [10]。乳酸化通过组蛋白乳酸化修饰激活核因子- κ B (nuclear factor kappa-B, NF- κ B)信号通路，加剧炎症反应[11]。乳酸化可能通过调节乙醛脱氢酶 2 (aldehyde dehydrogenase 2, ALDH2)的 K52 位点修饰，影响线粒体功能，加剧氧化应激相关的凝血紊乱[12]。高乳酸化表型的脓症患者往往表现出更严重的炎症反应、更长住院时间和更高的死亡率[7] [13]。基于以上研究，了解乳酸化在脓毒症中器官损伤的作用机制对于临床决策至关重要。本文就乳酸化在脓毒症相关器官损伤中的作用机制作一简要概述。

2. 乳酸化在脓毒症肺损伤中的作用机制

2.1. 表观遗传调控

脓毒症状态下，肺作为机体重要的气体交换器官，易率先受到炎症因子与代谢紊乱的影响，而乳酸化修饰在此过程中扮演关键角色。乳酸化修饰通过影响基因转录参与脓毒症相关急性肾损伤和肺损伤的病理过程[10] [14]。缪等研究发现，脓毒症后乳酸可通过组蛋白乳酸化上调甲基转移酶样蛋白 3 (Methyltransferase-like protein 3, METTL3)表达进而调控长链脂肪酰辅酶 A 合成酶 4 (Acyl-Coenzyme A Synthetase Long Chain Family, Member 4, ACSL4)的 m6A 修饰水平，促进肺泡上皮细胞铁死亡，加剧脓毒症肺损伤[15]。

2.2. 炎症与免疫

Gong 等[16]通过动物实验证实，脓毒症期间积累的乳酸会促进巨噬细胞中冷诱导 RNA 结合蛋白

(Cold-inducible RNA-binding protein, CIRP)的乳酸化, 从而导致 CIRP 的释放。胞外 CIRP 通过 Toll 样受体 4 介导的内吞途径被肺血管内皮细胞内化后, 会竞争性地与 Z-DNA 结合蛋白 1 (Z-DNA binding protein 1, ZBP1)结合, 并有效地阻断 ZBP1 与三联基序蛋白 32 (Tripartite Motif Containing 32, TRIM32)之间的相互作用, 而 TRIM32 是一种靶向针对 ZBP1 进行蛋白酶体降解的 E3 泛素连接酶。这种干扰机制稳定了 ZBP1, 从而增强了 ZBP1-受体相互作用蛋白激酶 3 依赖性肺血管内皮细胞泛凋亡, 加剧肺损伤。

2.3. 内皮细胞损伤

脓毒症中, 肺微血管内皮细胞的乳酸化修饰(如 H3K14 乳酸化)通过调控铁死亡和血管屏障破坏, 加剧肺损伤, 而抑制糖酵解可降低 H3K14 乳酸化水平, 改善血管功能[8]。巨噬细胞在脓毒症诱导的急性肺损伤的发展中起关键作用, 在这一过程中, 细胞外囊泡充当关键介质。巨噬细胞源性的细胞外囊泡包装的鸟苷酸结合蛋白 2 通过促进肺血管内皮细胞的铁死亡, 进而加重脓毒症诱导的急性肺损伤[17]。另一项研究表明, 组蛋白 H3K18 的乳酸化与早期生长反应蛋白 1 协同促进脓毒症诱导的急性肺损伤中内皮糖萼的降解, 加剧内皮细胞功能障碍[18]。

3. 乳酸化在脓毒症相关肾损伤中的作用机制

脓毒症肺损伤引发的呼吸功能障碍会导致全身缺氧与代谢产物蓄积, 而肾脏作为机体代谢废物排泄的核心器官, 在脓毒症病程中易因缺氧与炎症扩散受到二次打击, 乳酸化修饰同样参与了脓毒症相关肾损伤的病理过程。

3.1. 基因转录调控与线粒体损伤

研究显示, 组蛋白 H3K18 乳酸化在脓毒症相关肾损伤中显著升高, 并通过富集于 Ras 同源基因家族成员 A (Ras homolog gene family member A, RhoA)等启动子区域, 激活 Ras 同源基因家族蛋白 A (Ras homolog gene A, Rho A)/Rho 相关卷曲螺旋结合蛋白激酶(Rho-associated coiled coil-forming protein kinase, ROCK)/埃兹蛋白(Ezrin)信号通路, 进而激活 NF- κ B, 促进炎症、细胞凋亡, 加剧肾功能障碍[14]。乳酸通过促进 Ezrin K263 位点的乳酸化, 增强 Ezrin 的功能, 进而加剧了脓毒症诱导的肾损伤。研究表明, ALDH2 的 K52 位点乳酸化是脓毒症相关肾损伤的关键机制之一。ALDH2 是一种线粒体酶, 可将乙醛代谢成无毒乙酸, 影响线粒体氧化 ATP 的产生和活性氧的生成。ALDH2 可抑制糖酵解和乳酸的产生, 通过与急性肾损伤中的过氧化物酶体增殖物激活受体 γ 共激活因子 1- α 相互作用来减轻线粒体功能障碍。ALDH2 乳酸化会抑制其去乙酰化活性, 导致线粒体功能障碍和肾小管细胞凋亡。Li 等[12]发现, 在脓毒症相关急性肾损伤患者和小鼠模型中, 肾组织乳酸水平和泛乳酸化水平显著升高, 尤其在近端肾小管损伤细胞中乳酸化活性增强。乳酸代谢紊乱通过抑制丙酮酸脱氢酶的活性, 导致线粒体功能受损、ATP 耗竭和活性氧积累, 加剧肾小管损伤[19] [20]。

3.2. 炎症及免疫

高迁移率族蛋白 B1 (High mobility group box1, HMGB1)是损伤相关分子模式的重要分子, 在调节炎症中起着重要作用。研究表明[21], 脓症患者血 HMGB1 水平显著升高, 与病情严重程度及死亡率呈正相关。此外, 脓毒症相关肾损伤患者血乳酸水平升高与 HMGB1 水平升高相关。在小鼠模型中, 乳酸可增加 HMGB1 的表达, 促进中性粒细胞胞外诱捕网的形成, 并通过环鸟苷酸合酶 - 干扰素基因刺激因子(Cyclic Guanosine Monophosphate Adenosine Monophosphate Synthase-stimulator of interferon genes, cGAS-STING)信号通路加剧脓毒症相关肾损伤[22]。此外, 乳酸刺激 M1 巨噬细胞分泌外泌体, 导致 HMGB1 在细胞质中的积累和释放。这些研究表明 HMGB1 可能是脓毒症相关肾损伤治

疗干预的潜在靶标。

4. 乳酸化在脓毒症肝损伤中的作用机制

肾脏排泄功能受损会导致体内炎症因子与代谢毒素进一步滞留，而肝脏作为主要的解毒器官与代谢中心，在清除这些有害物质的过程中，自身也会因乳酸化修饰的异常调控而发生损伤。

4.1. 铁死亡及氧化应激

乳酸依赖的 H3K14 乳酸化通过调控内皮细胞铁死亡导致血管功能障碍，这一机制在脓毒症相关肺损伤中已被证实，可能同样适用于肝损伤[10]。氧化应激是脓毒症诱导的肝损伤的常见机制，活性氧的过量产生是氧化应激的主要原因。过多的活性氧可以触发炎症级联反应，释放促炎因子加剧炎症反应，从而导致肝损伤[23]。脂质运载蛋白-2 (Lipocalin-2, LCN2) 是一种分泌的糖蛋白，可诱导各种趋化因子参与炎症反应[24]。LCN2 在各种细胞应激条件下被上调，是铁代谢、氧化应激和炎症反应的重要调节剂[25]。在脓毒症小鼠中，抑制铁死亡和铁超负荷可能会减轻肝损伤，而 LCN2 表达降低则通过抑制铁死亡和减少氧化应激来缓解脓毒症肝损伤[26]。

4.2. 代谢重编程与免疫调节

脓毒症状态下糖酵解增强导致乳酸积累，通过乳酸化修饰糖酵解关键酶，形成正反馈循环，进一步加重代谢紊乱[8] [9]。巨噬细胞 M1 极化也受乳酸化调控，丹酚酸 B (Salvianolic acid B, Sal B) 通过下调乳酸脱氢酶 A 水平抑制巨噬细胞组蛋白乳酸化，从而减轻肝损伤[27]。

5. 乳酸化在脓毒症脑病中的作用机制

肝脏解毒功能下降会导致毒性物质入血并通过血脑屏障，而大脑作为对缺氧与毒性物质极为敏感的器官，乳酸化修饰在脓毒症脑病的发生中也具有重要作用。

5.1. 神经炎症

乳酸化通过调控小胶质细胞的 M1 型极化(促炎表型)参与脓毒症脑病的神经炎症过程。缺氧或脓毒症状态下，乳酸化修饰驱动小胶质细胞向 M1 型转化，释放促炎因子，导致海马神经元损伤和突触修剪异常[28]-[30]。此外，补体 C1q 的激活和突触修剪增加也与乳酸化介导的神经炎症相关[29]。

5.2. 分子与信号通路

研究证实[31]，N-乙酰转移酶 10 通过 γ -氨基丁酸受体 1 (γ -Aminobutyric Acid Receptor Type A, GABA_R1) mRNA 乙酰化介导脓毒症相关性脑病中的认知功能障碍。METTL3 介导的 mRNA m⁶A 修饰在脓毒症脑病中通过乳酸化依赖的机制促进神经元铁死亡，加剧认知功能障碍[15]。Wu 等[32]研究发现，乳酸化可能通过抑制沉默信息调节因子 2 相关酶 1 (Silent Information Regulator 2-Related Enzyme 1, SIRT1) 的活性，导致海马区认知功能受损，而 SIRT1 激动剂可改善脓毒症小鼠的认知缺陷。

6. 乳酸化在脓毒症心肌病中的作用机制

6.1. 代谢重编程与乳酸化调控

研究发现，脓毒症小鼠肺组织中乳酸和 H3K14 乳酸化水平升高，抑制糖酵解可减少乳酸化并改善内皮细胞功能障碍[10]。类似机制可能存在于心肌细胞中，乳酸通过乳酸化修饰调控代谢酶(如乳酸脱氢酶、单羧酸转运蛋白 1/4)的活性，加剧心肌能量代谢紊乱[8] [33]。

6.2. 免疫炎症调节

乳酸化通过修饰免疫相关蛋白(如 HMGB1)和信号通路(如 NF- κ B/NLRP3),调控巨噬细胞极化(M1/M2 型)和炎症因子释放。研究表明,信号转导与转录激活因子 1-Z-DNA 结合蛋白(Signal Transducer and Transcription Activator 1-Z-DNA binding protein 1, STAT1-ZBP1)轴可通过乳酸化促进炎症反应,加重心肌损伤[34] [35]。ZBP1 主要在巨噬细胞中表达,巨噬细胞衍生的 ZBP1 会加剧脂多糖诱导的心肌功能障碍和炎症细胞浸润。ZBP1 的缺失促进了巨噬细胞从 M1 到 M2 亚型的极化,从而减少炎症细胞浸润。此外,抑制热休克蛋白 A12A 可通过雷帕霉素靶蛋白信号通路减少自噬和炎症,从而缓解脓毒症心肌病[36]。

7. 乳酸化在脓毒症肠道功能障碍中的作用机制

7.1. 代谢-免疫失衡

脓毒症中糖酵解增强导致乳酸堆积,进一步通过乳酸化修饰反馈调节糖酵解关键酶(如血小板型磷酸果糖激酶、果糖-1,6-二磷酸醛缩酶 B),形成代谢重编程的恶性循环[7] [8]。而靶向糖酵解关键酶(如 6-磷酸果糖激酶-2/果糖双磷酸酶-2 同工酶 3)可减少乳酸积累,改善脓毒症小鼠肠道屏障功能[37]。此外,乳酸化修饰改变单核巨噬细胞的表现遗传状态,促进促炎因子(如 IL-6)释放,同时抑制肠道固有层 Treg 细胞功能,加剧肠道免疫失衡[9] [38]。临床上,益生菌和 L-缬氨酸可通过恢复肠道菌群平衡,降低乳酸水平,间接抑制乳酸化修饰,改善肠黏膜通透性,减轻乳酸化介导的肠损伤[39] [40]。

7.2. 肠道屏障损伤

乳酸通过修饰组蛋白(如 H3K18)和非组蛋白(如 Ezrin 蛋白 K263 位点),激活 Ras 同源基因家族(RhoA)/ROCK 信号通路,导致紧密连接蛋白泛素化降解,破坏肠上皮细胞间连接[14] [41]。此外,乳酸化通过上调早期生长反应蛋白 1 转录促进肝素酶表达,进一步加剧肠道微血管内皮细胞损伤[18]。乳酸化亦可通过调控糖酵解/H3K14 乳酸化/铁死亡轴,加重肠上皮细胞铁死亡和凋亡[10] [42]。同时,乳酸化修饰的 S100A11 和 CCNA2 基因通过调节单核巨噬细胞和 T 细胞的炎症反应驱动肠道损伤,与脓毒症预后相关[13]。

8. 临床意义与未来转化策略

8.1. 乳酸化作为生物标志物的可行性

就检测样本而言,脓毒症患者的血液、尿液及肾、肺等受累器官组织均适用,其中血液样本因获取方便且可满足动态监测需求,尿液样本则凭借无创优势降低患者负担;技术方法上,既能通过质谱分析精准检测组蛋白与非组蛋白的乳酸化位点,也可借助免疫印迹法实现快速定性。这一生物标志物的潜在优势尤为突出,不仅能更早反映病情变化以弥补传统指标的滞后性,还可通过区分不同器官损伤的特异性乳酸化修饰,为精准诊断提供支持。

8.2. 乳酸化调控酶作为药物靶点的可能性

基于乳酸化修饰的调控机制,相关调控酶或成为药物研发的潜在靶点。潜在药物方面,靶向 SIRT1 激动剂能降低乳酸化水平以改善认知障碍;靶向策略上,可通过调控乳酸脱氢酶 A、METTL3 等酶的活性,阻断 NF- κ B、RhoA/ROCK 等乳酸化相关信号通路。从预期疗效来看,这类药物有望减轻炎症反应、保护器官功能并降低死亡率,但在不同患者的乳酸化表型差异可能影响药物疗效稳定性。

8.3. 基础研究走向临床应用的障碍和挑战

尽管乳酸化相关研究展现出良好前景,但从基础研究迈向临床应用仍面临诸多挑战。乳酸化修饰在

不同器官损伤中的特异性机制尚未完全阐明, 导致缺乏统一的检测标准, 影响临床应用的规范性; 而且现有检测技术成本高、操作复杂, 难以在基层医疗机构普及; 此外, 药物研发中如何实现对特定乳酸化位点的精准靶向、避免脱靶效应, 仍是亟待突破的技术问题。临床转化需依托大量多中心临床试验验证有效性与安全性, 而目前相关研究样本量较小, 证据强度不足, 难以支撑广泛临床应用。

综上所述, 乳酸化修饰在脓毒症相关器官损伤中的作用机制复杂, 或可为后续临床药物靶点开发、生物标志物应用等提供新的研究方向。在脓毒症患者中, 是否存在可以特异性调控病理性乳酸化而不影响生理性乳酸代谢的策略, 是未来我们需要考虑的问题之一, 仍需进一步探究其复杂的作用机制和临床转化挑战。

基金项目

延安市科学技术协会青年人才托举计划资助——乳酸清除率联合降钙素原清除率对脓毒性休克患者预后的价值分析[课题编号: 延市科协发(2022) 37 号]。

参考文献

- [1] Rudd, K.E., Johnson, S.C., Agesa, K.M., Shackelford, K.A., Tsoi, D., Kievlan, D.R., *et al.* (2020) Global, Regional, and National Sepsis Incidence and Mortality, 1990-2017: Analysis for the Global Burden of Disease Study. *The Lancet*, **395**, 200-211. [https://doi.org/10.1016/s0140-6736\(19\)32989-7](https://doi.org/10.1016/s0140-6736(19)32989-7)
- [2] Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., *et al.* (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, **315**, 801-810. <https://doi.org/10.1001/jama.2016.0287>
- [3] Evans L, Rhodes A, Alhazzani W, *et al.* (2021) Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Intensive Care Medicine*, **47**, 1181-1247.
- [4] Zhang, D., Tang, Z., Huang, H., Zhou, G., Cui, C., Weng, Y., *et al.* (2019) Metabolic Regulation of Gene Expression by Histone Lactylation. *Nature*, **574**, 575-580. <https://doi.org/10.1038/s41586-019-1678-1>
- [5] Fang, C., Ren, P., Bian, G., Wang, J., Bai, J., Huang, J., *et al.* (2023) Enhancing Spns2/S1P in Macrophages Alleviates Hyperinflammation and Prevents Immunosuppression in Sepsis. *EMBO Reports*, **24**, e56635. <https://doi.org/10.15252/embr.202256635>
- [6] Sangsuwan, R., Thuamsang, B., Pacifici, N., Tachachartvanich, P., Murphy, D., Ram, A., *et al.* (2025) Identification of Signaling Networks Associated with Lactate Modulation of Macrophages and Dendritic Cells. *Heliyon*, **11**, e42098. <https://doi.org/10.1016/j.heliyon.2025.e42098>
- [7] Wang, Y., Wei, A., Su, Z., Shi, Y., Li, X. and He, L. (2025) Characterization of Lactylation-Based Phenotypes and Molecular Biomarkers in Sepsis-Associated Acute Respiratory Distress Syndrome. *Scientific Reports*, **15**, Article No. 13831. <https://doi.org/10.1038/s41598-025-96969-6>
- [8] Sun, Z., Song, Y., Li, J., Li, Y., Yu, Y. and Wang, X. (2023) Potential Biomarker for Diagnosis and Therapy of Sepsis: Lactylation. *Immunity, Inflammation and Disease*, **11**, e1042. <https://doi.org/10.1002/iid3.1042>
- [9] Liu, S., Yang, T., Jiang, Q., Zhang, L., Shi, X., Liu, X., *et al.* (2024) Lactate and Lactylation in Sepsis: A Comprehensive Review. *Journal of Inflammation Research*, **17**, 4405-4417. <https://doi.org/10.2147/jir.s459185>
- [10] Gong, F., Zheng, X., Xu, W., Xie, R., Liu, W., Pei, L., *et al.* (2025) H3k141a Drives Endothelial Dysfunction in Sepsis-induced ARDS by Promoting SLC40A1/Transferrin-Mediated Ferroptosis. *MedComm*, **6**, e70049. <https://doi.org/10.1002/mco2.70049>
- [11] Ma, N., Wang, L., Meng, M., Wang, Y., Huo, R., Chang, G., *et al.* (2025) D-Sodium Lactate Promotes the Activation of Nf- κ B Signaling Pathway Induced by Lipopolysaccharide via Histone Lactylation in Bovine Mammary Epithelial Cells. *Microbial Pathogenesis*, **199**, Article 107198. <https://doi.org/10.1016/j.micpath.2024.107198>
- [12] Li, J., Shi, X., Xu, J., Wang, K., Hou, F., Luan, X., *et al.* (2025) Aldehyde Dehydrogenase 2 Lactylation Aggravates Mitochondrial Dysfunction by Disrupting PHB2 Mediated Mitophagy in Acute Kidney Injury. *Advanced Science*, **12**, e2411943. <https://doi.org/10.1002/advs.202411943>
- [13] Li, S., Shen, Y., Wang, C., Yang, J., Chen, M. and Hu, Y. (2024) Exploring the Prognostic and Diagnostic Value of Lactylation-Related Genes in Sepsis. *Scientific Reports*, **14**, Article No. 23130. <https://doi.org/10.1038/s41598-024-74040-0>
- [14] Qiao, J., Tan, Y., Liu, H., Yang, B., Zhang, Q., Liu, Q., *et al.* (2024) Histone H3K18 and Ezrin Lactylation Promote

- Renal Dysfunction in Sepsis-Associated Acute Kidney Injury. *Advanced Science*, **11**, e2307216. <https://doi.org/10.1002/adv.202307216>
- [15] Wu, D., Spencer, C.B., Ortoga, L., Zhang, H. and Miao, C. (2024) Histone Lactylation-Regulated METTL3 Promotes Ferroptosis via m6A-Modification on ACSL4 in Sepsis-Associated Lung Injury. *Redox Biology*, **74**, Article 103194. <https://doi.org/10.1016/j.redox.2024.103194>
 - [16] Gong, T., Wang, Q., Loughran, P.A., Li, Y., Scott, M.J., Billiar, T.R., *et al.* (2024) Mechanism of Lactic Acidemia-Promoted Pulmonary Endothelial Cells Death in Sepsis: Role for C1RP-ZBP1-Panoptosis Pathway. *Military Medical Research*, **11**, Article No. 71. <https://doi.org/10.1186/s40779-024-00574-z>
 - [17] Li, Z., Bu, Y., Wang, C., Yu, Y., Han, L., Liu, C., *et al.* (2025) Extracellular Vesicle-Packaged GBP2 from Macrophages Aggravates Sepsis-Induced Acute Lung Injury by Promoting Ferroptosis in Pulmonary Vascular Endothelial Cells. *Redox Biology*, **82**, Article 103614. <https://doi.org/10.1016/j.redox.2025.103614>
 - [18] Lu, Z., Fang, P., Li, S., Xia, D., Zhang, J., Wu, X., *et al.* (2024) Lactylation of Histone H3k18 and Egr1 Promotes Endothelial Glycocalyx Degradation in Sepsis-Induced Acute Lung Injury. *Advanced Science*, **12**, e2407064. <https://doi.org/10.1002/adv.202407064>
 - [19] An, S., Yao, Y., Hu, H., Wu, J., Li, J., Li, L., *et al.* (2023) PDHA1 Hyperacetylation-Mediated Lactate Overproduction Promotes Sepsis-Induced Acute Kidney Injury via Fis1 Lactylation. *Cell Death & Disease*, **14**, Article No. 457. <https://doi.org/10.1038/s41419-023-05952-4>
 - [20] Wu, Z., Liu, W.Q., Tang, L., Yuan, Q., Li, Y., Hu, H., *et al.* (2024) Lactate-Mitochondrial Crosstalk: A New Direction in the Treatment of Sepsis-Induced Acute Kidney Injury. *Cell Biology International*, **48**, 1621-1624. <https://doi.org/10.1002/cbin.12240>
 - [21] Li, L. and Lu, Y. (2021) The Regulatory Role of High-Mobility Group Protein 1 in Sepsis-Related Immunity. *Frontiers in Immunology*, **11**, Article ID: 601815. <https://doi.org/10.3389/fimmu.2020.601815>
 - [22] Wei, S., Dai, Z., Wu, L., Xiang, Z., Yang, X., Jiang, L., *et al.* (2025) Lactate-Induced Macrophage HMGB1 Lactylation Promotes Neutrophil Extracellular Trap Formation in Sepsis-Associated Acute Kidney Injury. *Cell Biology and Toxicology*, **41**, Article No. 78. <https://doi.org/10.1007/s10565-025-10026-6>
 - [23] Zuo, L., Prather, E.R., Stetskev, M., Garrison, D.E., Meade, J.R., Peace, T.I., *et al.* (2019) Inflammaging and Oxidative Stress in Human Diseases: From Molecular Mechanisms to Novel Treatments. *International Journal of Molecular Sciences*, **20**, Article 4472. <https://doi.org/10.3390/ijms20184472>
 - [24] Jang, H.M., Lee, J.Y., An, H.S., Ahn, Y.J., Jeong, E.A., Shin, H.J., *et al.* (2022) LCN2 Deficiency Ameliorates Doxorubicin-Induced Cardiomyopathy in Mice. *Biochemical and Biophysical Research Communications*, **588**, 8-14. <https://doi.org/10.1016/j.bbrc.2021.12.048>
 - [25] Huang, Y., Zhang, N., Xie, C., You, Y., Guo, L., Ye, F., *et al.* (2022) Lipocalin-2 in Neutrophils Induces Ferroptosis in Septic Cardiac Dysfunction via Increasing Labile Iron Pool of Cardiomyocytes. *Frontiers in Cardiovascular Medicine*, **9**, Article ID: 922534. <https://doi.org/10.3389/fcvm.2022.922534>
 - [26] Li, Y., Li, L., Zhang, Y., Yun, Q., Du, R., Ye, H., *et al.* (2025) Lipocalin-2 Silencing Alleviates Sepsis-Induced Liver Injury through Inhibition of Ferroptosis. *Annals of Hepatology*, **30**, Article 101756. <https://doi.org/10.1016/j.aohep.2024.101756>
 - [27] Hu, S., Yang, Z., Li, L., Yan, Q., Hu, Y., Zhou, F., *et al.* (2024) Salvianolic Acid B Alleviates Liver Injury by Regulating Lactate-Mediated Histone Lactylation in Macrophages. *Molecules*, **29**, Article 236. <https://doi.org/10.3390/molecules29010236>
 - [28] He, L., Yin, R., Hang, W., Han, J., Chen, J., Wen, B., *et al.* (2024) Oxygen Glucose Deprivation-Induced Lactylation of H3K9 Contributes to M1 Polarization and Inflammation of Microglia through TNF Pathway. *Biomedicines*, **12**, Article 2371. <https://doi.org/10.3390/biomedicines12102371>
 - [29] Chung, H., Wickel, J., Hahn, N., Mein, N., Schwarzbrunn, M., Koch, P., *et al.* (2023) Microglia Mediate Neurocognitive Deficits by Eliminating C1q-Tagged Synapses in Sepsis-Associated Encephalopathy. *Science Advances*, **9**, eabq7806. <https://doi.org/10.1126/sciadv.abq7806>
 - [30] Chen, L., Luo, S., Liu, T., Shuai, Z., Song, Y., Yang, Q., *et al.* (2025) Growth Differentiation Factor 15 Aggravates Sepsis-Induced Cognitive and Memory Impairments by Promoting Microglial Inflammatory Responses and Phagocytosis. *Journal of Neuroinflammation*, **22**, Article No. 44. <https://doi.org/10.1186/s12974-025-03369-8>
 - [31] Gao, S., Shen, R., Li, J., Jiang, Y., Sun, H., Wu, X., *et al.* (2024) N-Acetyltransferase 10 Mediates Cognitive Dysfunction through the Acetylation of Gaba_B1 mRNA in Sepsis-Associated Encephalopathy. *Proceedings of the National Academy of Sciences*, **121**, e2410564121. <https://doi.org/10.1073/pnas.2410564121>
 - [32] Li, H., Liu, Q., Zhu, C., Sun, X., Sun, C., Yu, C., *et al.* (2023) β -Nicotinamide Mononucleotide Activates NAD⁺/SIRT1 Pathway and Attenuates Inflammatory and Oxidative Responses in the Hippocampus Regions of Septic Mice. *Redox Biology*, **63**, Article 102745. <https://doi.org/10.1016/j.redox.2023.102745>

-
- [33] Liao, Y., Niu, L., Ling, J., Cui, Y., Huang, Z., Xu, J., *et al.* (2025) Turning Sour into Sweet: Lactylation Modification as a Promising Target in Cardiovascular Health. *Metabolism*, **168**, Article 156234. <https://doi.org/10.1016/j.metabol.2025.156234>
- [34] Shi, Y., He, L., Ni, J., Zhou, Y., Yu, X., Du, Y., *et al.* (2025) Myeloid Deficiency of Z-DNA Binding Protein 1 Restricts Septic Cardiomyopathy via Promoting Macrophage Polarisation Towards the M2-Subtype. *Clinical and Translational Medicine*, **15**, e70315. <https://doi.org/10.1002/ctm2.70315>
- [35] Wang, F., Xue, P., Wang, J., Liu, Y., Han, X. and Xing, J. (2025) Esmolol Upregulates the $\alpha 7$ nAChR/STAT3/NF- κ B Pathway by Decreasing the Ubiquitin and Increasing the ChAT+CD4⁺ T Lymphocyte to Alleviate Inflammation in Septic Cardiomyopathy. *International Immunopharmacology*, **148**, Article 114043. <https://doi.org/10.1016/j.intimp.2025.114043>
- [36] Li, Y., Zhang, X., Jiang, G., Min, X., Kong, Q., Liu, L., *et al.* (2025) Downregulation of HSPA12A Protects Heart against Sepsis through Suppressing mTOR-Mediated Inflammatory Response in Cardiomyocytes. *International Immunopharmacology*, **145**, Article 113721. <https://doi.org/10.1016/j.intimp.2024.113721>
- [37] Zhang, Y., Liu, Y., Xie, Z., Liu, Q., Zhuang, Y., Xie, W., *et al.* (2022) Inhibition of PFKFB Preserves Intestinal Barrier Function in Sepsis by Inhibiting NLRP3/GSDMD. *Oxidative Medicine and Cellular Longevity*, **2022**, Article ID: 8704016. <https://doi.org/10.1155/2022/8704016>
- [38] Zhu, L., Dou, Z., Wu, W., Hou, Q., Wang, S., Yuan, Z., *et al.* (2023) Ghrelin/GHSR Axis Induced M2 Macrophage and Alleviated Intestinal Barrier Dysfunction in a Sepsis Rat Model by Inactivating E2F1/NF- κ B Signaling. *Canadian Journal of Gastroenterology and Hepatology*, **2023**, Article ID: 1629777. <https://doi.org/10.1155/2023/1629777>
- [39] Wu, R., Xu, J., Zeng, H., Fan, Y., Li, H., Peng, T., *et al.* (2024) Golden Bifid Treatment Regulates Gut Microbiota and Serum Metabolites to Improve Myocardial Dysfunction in Cecal Ligation and Puncture-Induced Sepsis Mice. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, **1870**, Article 167049. <https://doi.org/10.1016/j.bbadis.2024.167049>
- [40] Chen, Y., Sun, K., Qi, Y., Tang, J., Zhu, H. and Wang, Z. (2024) L-Valine Derived from the Gut Microbiota Protects Sepsis-Induced Intestinal Injury and Negatively Correlates with the Severity of Sepsis. *Frontiers in Immunology*, **15**, Article ID: 1424332. <https://doi.org/10.3389/fimmu.2024.1424332>
- [41] Cheng, L., Feng, B., Xie, C., Chen, C. and Guo, L. (2025) Overexpression of miR-20a Targeting DUSP3 Inhibits OCLN Ubiquitination Levels and Alleviates Sepsis Induced Intestinal Barrier Dysfunction. *In Vitro Cellular & Developmental Biology-Animal*, **61**, 459-471. <https://doi.org/10.1007/s11626-025-01052-z>
- [42] Cao, Y., Qiao, Y., Wang, Z., Chen, Q., Qi, Y., Lu, Z., *et al.* (2023) The Polo-Like Kinase 1-Mammalian Target of Rapamycin Axis Regulates Autophagy to Prevent Intestinal Barrier Dysfunction during Sepsis. *The American Journal of Pathology*, **193**, 296-312. <https://doi.org/10.1016/j.ajpath.2022.11.008>