

脓毒症相关心肌损伤代谢失调与免疫调节机制的研究进展

谢冰卿¹, 陈雪梅^{2*}

¹重庆医科大学第一临床医学院, 重庆

²重庆医科大学附属第一医院重症医学科, 重庆

收稿日期: 2026年1月12日; 录用日期: 2026年2月6日; 发布日期: 2026年2月24日

摘要

脓毒症相关心肌损伤(Sepsis-Induced Myocardial Dysfunction, SIMD)是导致脓症患者病死率显著升高的关键因素之一。近年来,随着代谢失调与免疫调节机制研究的深入,越来越多的证据表明这两者在SIMD的发病机制中起着核心作用。SIMD中心肌细胞代谢异常表现为能量供应不足、线粒体功能障碍及代谢产物积累,直接影响心肌收缩和舒张功能。同时,免疫细胞的激活及炎症因子的释放通过复杂的信号通路调控心肌炎症反应和细胞损伤。本文综述了脓毒症过程中代谢与免疫调节的相互作用,重点分析了代谢失调如何影响免疫反应,以及免疫调节对心肌代谢状态的反馈作用。结合最新基础和临床研究进展,探讨了代谢与免疫交互机制在SIMD中的具体表现及其潜在治疗靶点,旨在为该领域的深入研究和临床干预提供理论支持和新思路。

关键词

脓毒症, 心肌损伤, 代谢失调, 免疫调节, 炎症反应, 线粒体功能

Research Progress on Metabolic Disorders and Immune Regulatory Mechanisms in Sepsis-Induced Myocardial Dysfunction

Bingqing Xie¹, Xuemei Chen^{2*}

¹The First Clinical Medical College, Chongqing Medical University, Chongqing

²Department of Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing

*通讯作者。

文章引用: 谢冰卿, 陈雪梅. 脓毒症相关心肌损伤代谢失调与免疫调节机制的研究进展[J]. 临床医学进展, 2026, 16(2): 2962-2971. DOI: 10.12677/acm.2026.162707

Abstract

Sepsis-Induced Myocardial Dysfunction (SIMD) is one of the key factors leading to a significant increase in mortality among sepsis patients. In recent years, with the deepening research into metabolic disorders and immune regulatory mechanisms, an increasing amount of evidence has shown that both play a central role in the pathogenesis of SIMD. The metabolic abnormalities in SIMD cardiomyocytes are characterized by insufficient energy supply, mitochondrial dysfunction, and accumulation of metabolic products, which directly affect myocardial contraction and relaxation functions. At the same time, the activation of immune cells and the release of inflammatory factors regulate myocardial inflammatory responses and cellular damage through complex signaling pathways. This article reviews the interaction between metabolism and immune regulation during the process of sepsis, focusing on how metabolic disorders affect immune responses, as well as the feedback effect of immune regulation on myocardial metabolic status. Combining the latest basic and clinical research progress, it explores the specific manifestations and potential therapeutic targets of the interaction mechanisms between metabolism and immunity in SIMD, aiming to provide theoretical support and new ideas for in-depth research and clinical interventions in this field.

Keywords

Sepsis, Myocardial Injury, Metabolic Disorder, Immune Regulation, Inflammatory Response, Mitochondrial Function

Copyright © 2026 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 前言

脓毒症是一种由感染引发的全身炎症反应综合征,常伴随多器官功能障碍,严重时可导致多个器官衰竭,死亡率极高[1]。脓毒症相关心肌损伤(SIMD)作为脓毒症最常见且严重的并发症之一,其发病机制涉及多方面复杂因素的相互作用[2],代谢失调与免疫调节在SIMD中的作用引起了广泛关注。一项回顾性研究显示,在重症监护病房收治的脓毒症相关心肌损伤患者中,心肌损伤标志物的动态变化与患者28天内的死亡风险显著相关,心肌损伤评分越高,患者死亡率越大[3]。这表明心肌损伤是脓毒症患者预后不良的重要指标,仍需深入揭示其分子机制以指导临床治疗。传统观点认为,SIMD主要是炎症因子直接损伤心肌细胞所致,炎症介质如TNF- α 、IL-1 β 等在病理过程中起关键作用[4]。相关研究发现,脓毒症过程中炎症介质的异常表达加剧了心肌细胞的氧化应激和凋亡,导致心肌功能障碍[5][6]。然而,单纯的炎症学说难以解释SIMD的全部病理过程,越来越多的证据表明代谢紊乱在其中发挥重要作用。

代谢方面,在正常情况下心肌细胞对能量需求极高,以脂肪酸氧化为主,兼顾糖代谢,保证充足的ATP供应[7]。脓毒症时,心肌线粒体结构破坏、呼吸链功能受损,导致ATP合成减少,进而引起心肌收缩功能下降[8][9]。研究显示,脓毒症模型小鼠心肌线粒体内,呼吸控制比及复合物I活性明显降低,代谢通路紊乱,促使心肌线粒体功能受损[10]。此外,代谢产物如乳酸在脓症患者中升高,乳酸不仅是能量代谢的产物,还通过对免疫细胞的调控介导免疫失衡,影响病情进展[11][12]。免疫调节方面,脓毒症导致免疫系统功能紊乱,既表现为炎症反应过度,又伴随免疫抑制[13]。免疫细胞如巨噬细胞、T细胞、

自然杀伤细胞等数量及功能异常,参与炎症介质的产生和释放,调控心肌损伤程度[14][15]。单细胞转录组研究揭示脓毒症不同免疫细胞亚群的异质性及其代谢状态变化,部分免疫细胞表现出代谢重编程,如糖酵解增强,促使炎症反应加剧[16][17]。此外,免疫细胞表面抑制性受体 PD-1 及其配体 PD-L1 的表达上调,介导免疫抑制状态的形成[18]。

代谢与免疫调节机制的交互作用是脓毒症相关心肌损伤的关键环节[19]。代谢紊乱导致能量供应不足,加重免疫细胞功能障碍;而免疫细胞释放的炎症介质又可进一步损伤心肌和线粒体功能,形成恶性循环[20][21]。研究发现,调控关键代谢通路或增强线粒体功能可改善免疫功能及心肌损伤,如通过激活 SIRT3、AMPK 等信号通路促进线粒体生物合成和抗氧化,有助于缓解 SIMD [15][22]。基于此,代谢调控和免疫调节成为 SIMD 治疗的新兴靶点。例如,植物提取物 lobetyolin、umbelliferone 等能抑制炎症反应,调节氧化应激,保护心肌[17][23];靶向 VDAC2 蛋白的 malonylation 修饰调节线粒体铁死亡,有望减轻心肌损伤[24];利用纳米技术靶向调控炎症介质,协同减轻心肌炎症和免疫紊乱[25]。此外,免疫细胞代谢重编程的调控剂如 ATF4、PGK1 等分子为免疫代谢治疗提供了潜在方向[23][26]。

综上,脓毒症相关心肌损伤是代谢失调与免疫调节交互作用的结果。代谢紊乱导致能量供应不足和线粒体功能障碍,免疫细胞功能失调加剧炎症反应,形成恶性循环。未来研究应重点揭示代谢与免疫调节的相互机制,开发靶向代谢通路和免疫调节的新型治疗策略,以改善脓毒症患者心肌损伤的预后。

2. 脓毒症相关心肌损伤中的代谢失调机制

2.1. 能量代谢异常及其对心肌功能的影响

脓毒症状态下,心肌细胞的能量代谢发生显著异常,主要表现为葡萄糖代谢和脂肪酸氧化均受到抑制,导致 ATP 生成不足,进而影响心肌收缩功能[27]。心肌细胞通常依赖有氧代谢产生 ATP,以维持正常的收缩和舒张功能[28]。然而,脓毒症过程中,由于炎症反应及组织低灌注,心肌细胞发生代谢重编程,逐渐从高效的有氧代谢转向低效的无氧糖酵解,导致能量供应不足,促进心肌功能障碍[29]。同时,乳酸导致细胞内酸性环境加剧,诱发酸中毒,破坏细胞内电解质平衡和电生理稳定性,进一步损伤心肌细胞,降低心肌收缩性[30]。此外,脂肪酸代谢障碍、脂肪酸氧化率降低及脂肪酸中间代谢产物积累,进一步损害线粒体功能,加剧能量代谢异常[31]。代谢重编程不仅降低了 ATP 生成效率,还通过调节细胞内信号通路如 AMPK 和 mTOR 影响心肌细胞的代谢适应能力和免疫反应,促进心肌损伤的发生和发展[32][33]。因此,脓毒症引起的能量代谢异常是心肌功能减弱的重要机制,为临床诊断和治疗提供了潜在的代谢靶点。

2.2. 线粒体功能障碍及氧化应激

线粒体作为心肌细胞能量代谢的核心,其功能障碍是脓毒症相关心肌损伤的重要病理基础[34]。脓毒症诱导下,线粒体膜电位下降,呼吸链复合物活性受损,导致电子传递受阻,ATP 合成减少[35]。线粒体功能不全促进活性氧(ROS)过度生成,引发氧化应激。过多的 ROS 损伤细胞膜、蛋白质和线粒体 DNA,诱导心肌细胞凋亡和坏死,加重心肌损伤[36][37]。线粒体自噬(mitophagy)是维持线粒体质量控制的重要机制[38]。脓毒症状态下,mitophagy 调节失衡,受损线粒体无法及时清除,导致受损线粒体积累,进一步加剧代谢异常和细胞损伤[39][40]。有研究显示,Narciclasine 通过促进 JNK 依赖的自噬通路发挥心肌保护作用,提示调控 mitophagy 是缓解脓毒症心肌损伤的潜在策略[39]。此外,氧化应激与细胞凋亡信号通路交织,线粒体膜通透性改变促进细胞色素 c 释放,激活半胱天冬酶级联反应,导致心肌细胞凋亡[37]。因此,线粒体功能障碍和氧化应激共同构成脓毒症心肌损伤的重要病理过程,靶向线粒体保护和抗氧化治疗具有重要的临床意义。

2.3. 代谢产物及信号分子在心肌损伤中的作用

脓毒症心肌损伤过程中,代谢产物如乳酸、脂肪酸中间产物及ATP降解产物不仅反映能量代谢状态,同时参与调节炎症反应和细胞凋亡。乳酸堆积激活酸敏感信号通路,加重细胞内酸中毒和电解质紊乱[30]。脂肪酸代谢异常产生的脂肪酸中间产物可激活炎症介质释放,促进心肌细胞损伤。ATP降解产物作为细胞能量状态的信号分子,调节免疫细胞活性和炎症因子表达,影响心肌损伤修复过程[31]。代谢相关信号通路如AMPK、mTOR和HIF-1 α 在脓毒症心肌损伤中扮演调控代谢适应和免疫反应的关键角色。AMPK作为能量感应器,促进葡萄糖摄取和脂肪酸氧化,维持能量代谢平衡,其活性降低与心肌功能障碍密切相关[33]。mTOR通路调节细胞生长和代谢,脓毒症中其异常激活参与心肌细胞凋亡和炎症[32]。HIF-1 α 调控缺氧适应,促进糖酵解代谢,脓毒症状态下其表达改变影响心肌代谢重编程[33]。通过调控这些信号分子,可改善脓毒症心肌代谢失调,减轻心肌损伤,促进修复[32][33]。因此,代谢产物及其信号通路在脓毒症相关心肌损伤中起到桥梁作用,成为潜在的治疗靶点。

3. 脓毒症相关心肌损伤中的免疫调节机制

3.1. 免疫细胞的激活与心肌炎症反应

脓毒症状态下,巨噬细胞、单核细胞及中性粒细胞被病原体相关分子模式(PAMPs)和炎症介质激活,释放大量促炎因子,如肿瘤坏死因子- α (TNF- α)、白细胞介素-1 β (IL-1 β)、白细胞介素-6(IL-6)等,这些炎症介质直接损伤心肌细胞,导致心肌功能障碍[3]。免疫细胞大量浸润心肌组织,引发局部炎症反应,破坏心肌细胞结构,促进心肌细胞凋亡与坏死,加剧心肌损伤[39]。此外,巨噬细胞在炎症微环境中发生表型转换,M1型巨噬细胞表现为促炎表型,分泌大量炎症介质,维持炎症状态;而M2型巨噬细胞则具有抗炎和组织修复功能,其比例的变化影响炎症的持续与缓解[41]。也有相关研究显示,IL4I1作为一种免疫代谢酶,能够促进巨噬细胞的抗炎极化,减轻炎症反应,从而保护心肌[42]。同时,脓毒症诱导的免疫细胞激活伴随代谢重编程,免疫细胞的代谢状态(如糖酵解增强和氧化磷酸化抑制)决定其表型及功能,进一步影响炎症反应的强度和持续时间[43]。因此,免疫细胞的激活、浸润及表型转换形成复杂的调节网络,主导着脓毒症相关心肌损伤中的炎症反应。

3.2. 炎症因子与免疫信号通路

脓毒症中释放的炎症因子通过激活多条免疫信号通路调控心肌细胞的炎症反应和凋亡过程[44]。NF- κ B信号通路是调控炎症基因表达的核心通路,炎症因子如TNF- α 和IL-1 β 可激活NF- κ B,促进心肌细胞产生更多促炎介质,加剧炎症损伤[39]。此外,JAK/STAT通路在脓毒症炎症反应中也具有重要作用,IL-6等炎症因子通过JAK/STAT信号增强心肌细胞的炎症反应及凋亡[45]。炎症介质还可导致心肌细胞内钙稳态失衡,破坏心肌收缩功能,造成心肌收缩障碍[3]。免疫检查点分子如PD-1/PD-L1在调节免疫耐受和炎症反应中发挥着关键作用,其表达变化与脓毒症心肌损伤的免疫调控密切相关[46]。例如,PD-1/PD-L1轴通过抑制T细胞过度活化,减少炎症介质释放,保护心肌免受免疫介导的损伤[46]。因此,炎症因子与信号通路共同构成调控脓毒症相关心肌炎症和细胞凋亡的复杂网络,成为潜在的治疗靶点。

3.3. 免疫代谢调节及其在心肌保护中的作用

免疫细胞的代谢状态直接影响其功能和炎症表型,免疫代谢调节在脓毒症相关心肌损伤中具有重要意义[47]。脓毒症条件下,免疫细胞经历代谢重编程,糖酵解增强以满足快速能量需求,而氧化磷酸化则相对降低,这种代谢转变促进了促炎表型的维持[43]。有研究显示,部分代谢产物如乳酸还具有免疫调节功能,乳酸通过调控免疫细胞的活化状态和炎症因子的产生,影响炎症反应的强度和持续时间[43]。同时

有部分研究发现, 调控免疫细胞代谢的关键酶和信号分子, 如 AMPK、SIRT3 等, 也参与调节免疫细胞功能和心肌保护[48][49]。例如, AMPK 激活有利于增强自噬和抑制炎症, 减轻心肌损伤[33]。免疫代谢的调节为脓毒症相关心肌损伤的免疫治疗提供了新的潜在靶点, 通过精准调控免疫细胞的代谢状态, 有望实现炎症的有效控制和心肌保护[43]。综上, 免疫代谢调节不仅影响免疫细胞的功能, 还通过代谢信号调控炎症反应, 为脓毒症心肌损伤的治疗开辟了新方向。

4. 代谢失调与免疫调节的相互作用及在脓毒症心肌损伤中的影响

4.1. 代谢异常促进免疫炎症反应

脓毒症相关心肌损伤(SIMD)中, 代谢失调是促进免疫炎症反应的重要因素。代谢异常常导致心肌细胞内能量供应不足和氧化应激水平升高, 这些变化直接激活免疫细胞, 促进炎症因子的释放[50]。具体来说, 代谢产物不仅是能量的载体, 还作为信号分子调节免疫细胞的活性及炎症反应的程度[51]。有研究显示, 脂肪酸和葡萄糖代谢产物通过自由脂肪酸受体和 AMPK/mTOR 信号通路调节免疫反应, 影响炎症因子的表达, 从而加剧全身及心肌局部的炎症状态[52]。此外, 核苷酸代谢途径的调控与细胞功能密切相关, Akt、mTORC1 等信号网络能调节核苷酸合成, 进一步影响免疫细胞的增殖与功能[53]。代谢异常诱导的氧化应激不仅破坏心肌细胞的线粒体功能, 还通过促进炎症介质如 TNF- α 和 IL-6 的释放, 激活免疫系统, 形成炎症放大效应[39]。综上, 代谢失调通过多种机制激活免疫细胞, 加剧炎症反应, 导致了脓毒症心肌损伤的发生与发展。

4.2. 免疫炎症反应加剧代谢紊乱

代谢失调可通过多条路径加剧免疫功能障碍与炎症反应, 而免疫炎症反应反过来会进一步加重心肌细胞代谢紊乱, 形成恶性循环。炎症因子如 TNF- α 、IL-6 等通过影响线粒体功能和代谢酶活性, 导致线粒体呼吸链受损和能量代谢障碍, 心肌细胞表现为能量代谢衰竭[48]。此外, 免疫细胞释放的细胞因子可诱导心肌细胞代谢重编程, 使细胞能量代谢偏向糖酵解等低效路径, 进一步加剧氧化应激和炎症反应[37]。有研究发现, ER 应激途径中的 IRE1 α -XBP1 信号在免疫细胞中被激活, 促进巨噬细胞的高代谢状态, 导致炎症因子过度分泌, 加重代谢失衡及心肌损伤[54]。此外, 免疫细胞的代谢重塑不仅影响心肌细胞, 还通过分泌炎症介质促进心肌细胞凋亡和铁死亡, 加剧心肌功能障碍[55]。因此, 免疫炎症反应不仅是代谢紊乱的结果, 更是其促进因子, 二者相互作用共同推动脓毒症心肌损伤的进程。

4.3. 代谢 - 免疫的特征性差异作用

脓毒性心肌损伤(SIMD)的经典病理生理过程呈现出动态演变的特征, 经典上可划分为三个相互关联的阶段: 过度炎症期、免疫抑制期以及修复期[56]。在早期过度炎症期, 心脏微环境以促炎免疫细胞的浸润为主。循环中的中性粒细胞被大量招募至心脏, 并通过形成中性粒细胞胞外诱捕网(NETs)加剧心肌损伤和炎症[57]。在代谢方面, 即使在氧气充足的情况下也优先进行有氧糖酵解(Warburg 效应), 以满足快速能量需求和生物合成需求。这一代谢转变是免疫细胞从静息状态向活化状态转变的关键, 驱动了其分化、迁移和免疫应答[58]。代谢物层面, 乳酸和琥珀酸大量积累。乳酸不仅是糖酵解的终产物, 其累积还能通过表观遗传修饰(如组蛋白乙酰化)调控炎症基因表达[59]。

随着疾病进入免疫抑制期, 促炎细胞如中性粒细胞和 M1 型巨噬细胞减少或功能受抑制。免疫细胞的代谢特征发生根本性转变, 从过度活跃的糖酵解转向普遍的代谢抑制和线粒体功能障碍, 这直接导致了免疫细胞的功能耗竭和宿主防御能力的下降[15]。在脓毒症等病理状态下, 常伴有严重的线粒体损伤, 表现为线粒体膜电位降低、活性氧(ROS)泄漏和线粒体碎片化增加, 导致 ATP 生成不足和功能受损[60]。

此阶段心脏处于一种“麻痹”状态,虽然全身炎症可能减弱,但心肌的修复和再生能力也受到抑制,易发生继发感染和持续的能量代谢障碍[61]。

进入恢复期后,心脏微环境的主导细胞类型转变为与组织修复和重塑相关的群体。此阶段的特征是从炎症期的糖酵解优势和高分解代谢,转向氧化代谢的重建与合成代谢的增强,以支持抗炎和修复性细胞的功能[15]。在代谢物层面,修复期会出现一些具有抗炎和表观遗传调节作用的代谢物水平升高[62]。修复型巨噬细胞(如 M2c 型)活性增强,它们通过清除凋亡细胞碎片、分泌抗炎因子和促修复介质(如转化生长因子- β)来促进炎症消退[63]。修复期的代谢重编程是一个协调的能量代谢重建和合成代谢增强的过程,关键代谢酶和代谢物的变化共同驱动了免疫细胞向抗炎、修复表型的转变,并可能通过表观遗传机制巩固这种修复状态,为组织愈合和免疫稳态的恢复奠定基础。

4.4. 代谢 - 免疫互作的治疗潜力

鉴于代谢与免疫调节在脓毒症心肌损伤中的密切交织,联合针对代谢路径和免疫调控的治疗策略成为研究热点。有研究发现,激活 AMPK 通路可恢复线粒体功能,促进自噬,减轻氧化应激,从而改善心肌细胞代谢状态,降低炎症反应[33] [49]。在免疫调节方面,抑制过度炎症反应和调控免疫细胞极化(如促进巨噬细胞 M2 极化)有助于缓解心肌损伤[35]。新兴疗法包括代谢调节剂(如鲁丁宁、Puerarin)和免疫调节剂的联合应用,显示出改善 SIMD 预后的潜力[64]。此外,有研究发现,针对铁死亡调控通路的干预,如调节 GPX4 和铁稳态,能减轻心肌细胞的损伤[36]。在临床上,使用地西泮定、舒芬太尼等药物也显示出通过代谢和免疫双重调节保护心肌的效果[65]。在脓毒症等病理状态下,免疫细胞经历剧烈的代谢重编程,其产生的代谢中间产物(如乙酰辅酶 A、 α -酮戊二酸、S-腺苷甲硫氨酸)可作为表观修饰酶的辅助因子,从而将代谢状态与基因表达程序紧密耦合[66]。表观遗传调控对免疫细胞的激活、分化和功能具有重要影响,涉及巨噬细胞极化和 T 细胞分化,但代谢与表观遗传的交互作用具体机制尚需进一步阐明[67]。未来,深入理解代谢与免疫的互作机制,将为开发精准的联合治疗方案提供理论基础和实践指导。深入理解表观遗传机制对免疫细胞的特异性调控,揭示脓毒性心肌损伤等疾病中免疫代谢紊乱的分子基础,才能进一步促进脓毒症心肌损伤的有效干预。

5. 未来与展望

脓毒症相关心肌损伤作为临床上严重的并发症,其发生机制的复杂性和多样性一直是医学研究的重点。通过对现有文献的系统梳理可以看出,代谢失调与免疫调节机制在脓毒症心肌损伤中的核心作用不可忽视。代谢异常不仅直接影响心肌细胞的能量代谢和结构稳定性,导致心肌功能障碍,还通过调控免疫炎症反应,进而加剧心肌细胞的损伤和凋亡。这种双重作用机制揭示了代谢和免疫系统之间密不可分的交互关系,为理解脓毒症心肌损伤提供了新的视角。

免疫调节机制在心肌损伤发展过程中表现为炎症因子和免疫细胞的动态变化。过度炎症反应促使心肌细胞受到进一步损害,而适度的免疫反应则参与心肌组织的修复和恢复。不同研究在炎症介质种类和作用路径上存在一定差异,但总体趋势显示,精准调控免疫反应的强度和时机是控制心肌损伤的重要策略。此外,代谢通路的改变不仅影响免疫细胞功能,还可能通过代谢产物调节炎症反应,二者形成复杂的反馈调节网络。

面对目前研究中关于代谢异常和免疫调节在脓毒症心肌损伤中的具体机制存在的争议,未来的研究应更多聚焦于两者交叉机制的深入解析。多组学技术和单细胞分析等前沿方法的应用,有望揭示代谢与免疫信号通路的精细调控,为靶向治疗提供精准靶点。与此同时,临床上迫切需要开发结合代谢调节与免疫调控的综合治疗方案,以实现心肌保护和功能恢复的双重目标。脓毒症相关心肌损伤的治疗策略必

须突破传统单一靶点的限制, 注重代谢与免疫调节的协同作用。未来的临床试验应设计多维度干预措施, 评估其在水肌保护效果及整体患者预后中的价值。此外, 个体化治疗策略的制定尤为重要, 应根据患者的代谢状态和免疫反应特征, 制定精准的治疗方案, 以提高疗效并降低副作用。

综上所述, 代谢失调与免疫调节机制的交织是脓毒症相关水肌损伤发生和发展的关键环节。深入理解其相互作用不仅有助于丰富脓毒症水肌损伤的病理生理学知识体系, 更为临床治疗提供了新的思路和方向。未来的研究和临床实践应致力于整合代谢与免疫调节的优势, 推动靶向治疗策略的发展, 从而显著降低脓毒症患者的水肌损伤率与死亡率, 提升整体治疗效果和患者的生活质量。

参考文献

- [1] Fujishima, S. (2016) Organ Dysfunction as a New Standard for Defining Sepsis. *Inflammation and Regeneration*, **36**, Article No. 24. <https://doi.org/10.1186/s41232-016-0029-y>
- [2] Fan, D. and Wu, R. (2024) Mechanisms of the Septic Heart: From Inflammatory Response to Myocardial Edema. *Journal of Molecular and Cellular Cardiology*, **195**, 73-82. <https://doi.org/10.1016/j.yjmcc.2024.08.003>
- [3] Zhou, Y., Wang, G., Gao, X., Wang, S., Wang, S. and Tong, D. (2025) Sepsis-Associated Myocardial Injury: Incidence and Mortality. *Medicine*, **104**, e42513. <https://doi.org/10.1097/md.00000000000042513>
- [4] Zhang, N., Feng, H., Liao, H., Chen, S., Yang, Z., Deng, W., *et al.* (2017) Myricetin Attenuated LPS Induced Cardiac Injury *in Vivo* and *in Vitro*. *Phytotherapy Research*, **32**, 459-470. <https://doi.org/10.1002/ptr.5989>
- [5] Shao, R., Yang, Y., Zhang, Y., Zhao, S., Zheng, Z. and Chen, G. (2020) The Expression of Thioredoxin-1 and Inflammatory Cytokines in Patients with Sepsis. *Immunopharmacology and Immunotoxicology*, **42**, 280-285. <https://doi.org/10.1080/08923973.2020.1755309>
- [6] Wang, X., Yin, D., Sun, J., Zhang, L., Ye, Y. and Guo, Q. (2025) AR Deficiency Protects against Sepsis-Induced Acute Lung Injury by Inhibiting Macrophage M1 Polarization and Inflammatory Cytokine Secretion. *Inflammation*, **48**, 4203-4224. <https://doi.org/10.1007/s10753-025-02321-5>
- [7] Kawaguchi, S. and Okada, M. (2021) Cardiac Metabolism in Sepsis. *Metabolites*, **11**, Article No. 846. <https://doi.org/10.3390/metabo11120846>
- [8] Wang, P., Zheng, Y., Sun, J., Zhang, Y., Chan, W.K., Lu, Y., *et al.* (2024) Sepsis Induced Dysfunction of Liver Type 1 Innate Lymphoid Cells. *BMC Immunology*, **25**, Article No. 57. <https://doi.org/10.1186/s12865-024-00648-6>
- [9] You, J., Li, Y. and Chong, W. (2024) The Role and Therapeutic Potential of SIRT6 in Sepsis. *Frontiers in Immunology*, **15**, Article 57. <https://doi.org/10.3389/fimmu.2024.1394925>
- [10] Ren, J., Ren, B., Fu, T., Ma, Y., Tan, Y., Zhang, S., *et al.* (2024) Pyruvate Kinase M2 Sustains Cardiac Mitochondrial Integrity in Septic Cardiomyopathy by Regulating Phb2-Dependent Mitochondrial Biogenesis. *International Journal of Medical Sciences*, **21**, 983-993. <https://doi.org/10.7150/ijms.94577>
- [11] Zhang, T., Chen, L., Kueth, G., Shao, E., Wang, X., Ha, T., *et al.* (2024) Lactate's Impact on Immune Cells in Sepsis: Unraveling the Complex Interplay. *Frontiers in Immunology*, **15**, Article 1483400. <https://doi.org/10.3389/fimmu.2024.1483400>
- [12] Fan, S., Xie, L., Wang, R., Chen, Q. and Zhang, X. (2024) Novel Homozygous ADK Out-of-Frame Deletion Causes Adenosine Kinase Deficiency with Rare Phenotypes of Sepsis, Metabolites Disruption and Neutrophil Dysfunction. *Gene*, **914**, Article ID: 148313. <https://doi.org/10.1016/j.gene.2024.148313>
- [13] Mithal, L.B., Arshad, M., Swigart, L.R., Khanolkar, A., Ahmed, A. and Coates, B.M. (2021) Mechanisms and Modulation of Sepsis-Induced Immune Dysfunction in Children. *Pediatric Research*, **91**, 447-453. <https://doi.org/10.1038/s41390-021-01879-8>
- [14] Tao, X., Wang, J., Liu, B., Cheng, P., Mu, D., Du, H., *et al.* (2024) Plasticity and Crosstalk of Mesenchymal Stem Cells and Macrophages in Immunomodulation in Sepsis. *Frontiers in Immunology*, **15**, Article 1338744. <https://doi.org/10.3389/fimmu.2024.1338744>
- [15] Yang, K., Zhao, Q., Sun, Y., Lin, L. and Han, X. (2025) Mitochondrial Immunometabolism in Sepsis: Orchestrating Macrophage Polarization and Dysfunction. *European Journal of Medical Research*, **31**, Article No. 36. <https://doi.org/10.1186/s40001-025-03590-4>
- [16] Jin, S., Zhang, H., Lin, Q., Yang, J., Zeng, R., Xu, Z., *et al.* (2024) Deciphering the Immune-Metabolic Nexus in Sepsis: A Single-Cell Sequencing Analysis of Neutrophil Heterogeneity and Risk Stratification. *Frontiers in Immunology*, **15**, Article 1398719. <https://doi.org/10.3389/fimmu.2024.1398719>
- [17] Bati, Y.U., Sezer, M., Yilmaz, A., Baser, L., Guraslan, A., Bayram, P., *et al.* (2025) The Protective Effects of Dose-

- Dependent Umbelliferone Application on CLP-Induced Acute Lung Injury (ALI) Model. *Journal of Biochemical and Molecular Toxicology*, **39**, e70549. <https://doi.org/10.1002/jbt.70549>
- [18] Ruan, W.S., Feng, M.X., Xu, J., Xu, Y.G., Song, C.Y., Lin, L.Y., *et al.* (2020) Early Activation of Myeloid-Derived Suppressor Cells Participate in Sepsis-Induced Immune Suppression via PD-L1/PD-1 Axis. *Frontiers in Immunology*, **11**, Article 1299. <https://doi.org/10.3389/fimmu.2020.01299>
- [19] Wu, J., Sun, X. and Jiang, P. (2024) Metabolism-Inflammasome Crosstalk Shapes Innate and Adaptive Immunity. *Cell Chemical Biology*, **31**, 884-903. <https://doi.org/10.1016/j.chembiol.2024.04.006>
- [20] Salami, O.M., Habimana, O., Peng, J. and Yi, G. (2022) Therapeutic Strategies Targeting Mitochondrial Dysfunction in Sepsis-Induced Cardiomyopathy. *Cardiovascular Drugs and Therapy*, **38**, 163-180. <https://doi.org/10.1007/s10557-022-07354-8>
- [21] Liu, J., Zhou, G., Wang, X. and Liu, D. (2022) Metabolic Reprogramming Consequences of Sepsis: Adaptations and Contradictions. *Cellular and Molecular Life Sciences*, **79**, Article No. 456. <https://doi.org/10.1007/s00018-022-04490-0>
- [22] Lou, L., Li, J., Chen, W., Zhu, C.S., Qiang, X. and Wang, H. (2025) Pro-Dermcidin as an Emerging Regulator of Innate Immunity in Sepsis. *International Journal of Molecular Sciences*, **26**, Article No. 7643. <https://doi.org/10.3390/ijms26157643>
- [23] Liu, Y., Li, W., Lei, L., Zhou, Y., Huang, M., Li, Y., *et al.* (2024) Effects of PGK1 on Immunoinfiltration by Integrated Single-Cell and Bulk RNA-Sequencing Analysis in Sepsis. *Frontiers in Immunology*, **15**, Article 1449975. <https://doi.org/10.3389/fimmu.2024.1449975>
- [24] She, H., Tan, L., Du, Y., Zhou, Y., Guo, N., Zhang, J., *et al.* (2023) VDAC2 Malonylation Participates in Sepsis-Induced Myocardial Dysfunction via Mitochondrial-Related Ferroptosis. *International Journal of Biological Sciences*, **19**, 3143-3158. <https://doi.org/10.7150/ijbs.84613>
- [25] Wang, L., Ding, Y., Xue, F., Li, N., Du, Y., Wang, B., *et al.* (2026) Nanobody-Based High-Performance Multitarget Immunoadsorbents Protect against Sepsis by Concurrently Adsorbing Endotoxins and Inflammatory Cytokines. *Acta Biomaterialia*, **209**, 532-546. <https://doi.org/10.1016/j.actbio.2025.11.016>
- [26] Zhang, L., Shi, X., Qiu, H., Liu, S., Yang, T., Li, X., *et al.* (2023) Protein Modification by Short-Chain Fatty Acid Metabolites in Sepsis: A Comprehensive Review. *Frontiers in Immunology*, **14**, Article 1171834. <https://doi.org/10.3389/fimmu.2023.1171834>
- [27] Kuroshima, T., Kawaguchi, S. and Okada, M. (2024) Current Perspectives of Mitochondria in Sepsis-Induced Cardiomyopathy. *International Journal of Molecular Sciences*, **25**, Article No. 4710. <https://doi.org/10.3390/ijms25094710>
- [28] Hu, D., Linders, A., Yamak, A., Correia, C., Kijlstra, J.D., Garakani, A., *et al.* (2018) Metabolic Maturation of Human Pluripotent Stem Cell-Derived Cardiomyocytes by Inhibition of HIF1 α and LDHA. *Circulation Research*, **123**, 1066-1079. <https://doi.org/10.1161/circresaha.118.313249>
- [29] Bi, C.F., Liu, J., Yang, L.S. and Zhang, J.F. (2022) Research Progress on the Mechanism of Sepsis Induced Myocardial Injury. *Journal of Inflammation Research*, **15**, 4275-4290. <https://doi.org/10.2147/jir.s374117>
- [30] Han, Y.Y., Yang, J.L., Meng, H.M. and Wang, P. (2025) Identifying Risk Factors for Myocardial Injury in Elderly Patients with Sepsis. *Medical Science Monitor*, **31**, e947840. <https://doi.org/10.12659/msm.947840>
- [31] Xie, Y., Lv, H., Chen, D., Huang, P., Zhou, Z. and Wang, R. (2025) A Cd36-Based Prediction Model for Sepsis-Induced Myocardial Injury. *IJC Heart & Vasculature*, **57**, Article ID: 101615. <https://doi.org/10.1016/j.ijcha.2025.101615>
- [32] Mammedova, J.T., Sokolov, A.V., Freidlin, I.S. and Starikova, E.A. (2021) The Mechanisms of L-Arginine Metabolism Disorder in Endothelial Cells. *Biochemistry (Moscow)*, **86**, 146-155. <https://doi.org/10.1134/s0006297921020036>
- [33] Wu, B., Song, H., Fan, M., You, F., Zhang, L., Luo, J., *et al.* (2020) Luteolin Attenuates Sepsis-induced Myocardial Injury by Enhancing Autophagy in Mice. *International Journal of Molecular Medicine*, **45**, 1477-1487. <https://doi.org/10.3892/ijmm.2020.4536>
- [34] Fang, X. and Wang, J. (2018) Role of Mitochondrial Dysfunction in the Pathogenesis of Septic Cardiomyopathy. *Chinese Critical Care Medicine*, **30**, 189-192.
- [35] Zhao, L., Zhao, H., Sun, M., Chen, M., Wu, X., Deng, C., *et al.* (2022) Kudzu Celery Decoction Exerts Protection against Sepsis-Induced Myocardial Injury. *Oxidative Medicine and Cellular Longevity*, **2022**, Article ID: 2886932. <https://doi.org/10.1155/2022/2886932>
- [36] Wang, C., Yuan, W., Hu, A., Lin, J., Xia, Z., Yang, C., *et al.* (2020) Dexmedetomidine Alleviated Sepsis-Induced Myocardial Ferroptosis and Septic Heart Injury. *Molecular Medicine Reports*, **22**, 175-184. <https://doi.org/10.3892/mmr.2020.11114>
- [37] Xie, Y., Zhang, J., Jin, W., Tian, R. and Wang, R. (2021) Role of Thrombospondin-1 in Sepsis-Induced Myocardial Injury. *Molecular Medicine Reports*, **24**, Article No. 869. <https://doi.org/10.3892/mmr.2021.12509>
- [38] Kanki, T. and Okamoto, K. (2014) Assays for Autophagy II: Mitochondrial Autophagy. In: Xiao, W., Ed., *Yeast Protocols*,

- Springer, 165-173. https://doi.org/10.1007/978-1-4939-0799-1_11
- [39] Tang, R., Jia, L., Li, Y., Zheng, J. and Qi, P. (2021) Narciclasine Attenuates Sepsis-Induced Myocardial Injury by Modulating Autophagy. *Aging*, **13**, 15151-15163. <https://doi.org/10.18632/aging.203078>
- [40] Li, T., Chen, Y., Li, Y., Yao, Z. and Liu, W. (2021) Fam134b-Mediated Endoplasmic Reticulum Autophagy Protects against Sepsis Myocardial Injury in Mice. *Aging*, **13**, 13535-13547. <https://doi.org/10.18632/aging.202786>
- [41] Gao, P., Li, L., Chen, T., Li, N., Li, M., Zhang, H., *et al.* (2024) B-Arrestin2: An Emerging Player and Potential Therapeutic Target in Inflammatory Immune Diseases. *Acta Pharmacologica Sinica*, **46**, 2347-2362. <https://doi.org/10.1038/s41401-024-01390-w>
- [42] Dong, C., Shen, R., Ding, Y., Pan, C., Zhang, J., Yu, K., *et al.* (2025) IL4I1 Attenuates Myocardial Infarction by Inhibiting Macrophage Ferroptosis via the I3P/AHR/NRF2 Signaling Pathway. *International Immunopharmacology*, **165**, Article ID: 115393. <https://doi.org/10.1016/j.intimp.2025.115393>
- [43] DeBerge, M., Chaudhary, R., Schroth, S. and Thorp, E.B. (2023) Immunometabolism at the Heart of Cardiovascular Disease. *JACC: Basic to Translational Science*, **8**, 884-904. <https://doi.org/10.1016/j.jacbts.2022.12.010>
- [44] Jiang, L., Zhang, L., Yang, J., Shi, H., Zhu, H., Zhai, M., *et al.* (2022) 1-Deoxynojirimycin Attenuates Septic Cardiomyopathy by Regulating Oxidative Stress, Apoptosis, and Inflammation via the JAK2/STAT6 Signaling Pathway. *Biomedicine & Pharmacotherapy*, **155**, Article ID: 113648. <https://doi.org/10.1016/j.biopha.2022.113648>
- [45] Wang, J., Liu, T., Chen, X., Jin, Q., Chen, Y., Zhang, L., *et al.* (2021) Bazedoxifene Regulates Th17 Immune Response to Ameliorate Experimental Autoimmune Myocarditis via Inhibition of STAT3 Activation. *Frontiers in Pharmacology*, **11**, Article 613160. <https://doi.org/10.3389/fphar.2020.613160>
- [46] Ye, Z., Zhu, M., Li, S., Zhang, F., Ran, Y., Liu, C., *et al.* (2025) Multifunctional Nanoparticles for Immune Regulation and Oxidative Stress Alleviation in Myocarditis. *Journal of Controlled Release*, **381**, Article ID: 113607. <https://doi.org/10.1016/j.jconrel.2025.113607>
- [47] Pei, C., Zheng, H., Yang, K. and Song, N. (2025) Identification of Immunometabolism-Associated Genes and Immune Infiltration in Sepsis-Induced Cardiomyopathy Using Integrated Bioinformatics and Machine Learning Approaches. *Journal of International Medical Research*, **53**, 1-23. <https://doi.org/10.1177/03000605251395584>
- [48] Xin, T. and Lu, C. (2020) Sirt3 Activates AMPK-Related Mitochondrial Biogenesis and Ameliorates Sepsis-Induced Myocardial Injury. *Aging*, **12**, 16224-16237. <https://doi.org/10.18632/aging.103644>
- [49] Zhou, B., Zhang, J., Chen, Y., Liu, Y., Tang, X., Xia, P., *et al.* (2022) Puerarin Protects against Sepsis-Induced Myocardial Injury through AMPK-Mediated Ferroptosis Signaling. *Aging*, **14**, 3617-3632. <https://doi.org/10.18632/aging.204033>
- [50] El Hadi, H., Vettor, R. and Rossato, M. (2019) Cardiomyocyte Mitochondrial Dysfunction in Diabetes and Its Contribution in Cardiac Arrhythmogenesis. *Mitochondrion*, **46**, 6-14. <https://doi.org/10.1016/j.mito.2019.03.005>
- [51] Husted, A.S., Trauelsen, M., Rudenko, O., Hjorth, S.A. and Schwartz, T.W. (2017) GPCR-Mediated Signaling of Metabolites. *Cell Metabolism*, **25**, 777-796. <https://doi.org/10.1016/j.cmet.2017.03.008>
- [52] Liu, T., Zhang, Y. and Wang, C. (2021) Research Progress on the Roles and Mechanisms Underlying Metabolic Molecules Involved in Nutrition Therapy and Immune Regulation in Sepsis. *Chinese Critical Care Medicine*, **33**, 1017-1020.
- [53] Ali, E.S. and Ben-Sahra, I. (2023) Regulation of Nucleotide Metabolism in Cancers and Immune Disorders. *Trends in Cell Biology*, **33**, 950-966. <https://doi.org/10.1016/j.tcb.2023.03.003>
- [54] Lara-Reyna, S., Scambler, T., Holbrook, J., Wong, C., Jarosz-Griffiths, H.H., Martinon, F., *et al.* (2019) Metabolic Reprogramming of Cystic Fibrosis Macrophages via the IRE1 α Arm of the Unfolded Protein Response Results in Exacerbated Inflammation. *Frontiers in Immunology*, **10**, Article 1789. <https://doi.org/10.3389/fimmu.2019.01789>
- [55] Wang, X., Tian, Q., Li, M. and Liu, Y. (2025) METTL5 Triggers the Ferroptosis of Cardiomyocytes in Sepsis-Induced Myocardial Injury. *Free Radical Biology and Medicine*, **237**, 1-10. <https://doi.org/10.1016/j.freeradbiomed.2025.05.392>
- [56] Walley, K.R. (2014) Deeper Understanding of Mechanisms Contributing to Sepsis-Induced Myocardial Dysfunction. *Critical Care*, **18**, Article No. 137. <https://doi.org/10.1186/cc13853>
- [57] Wang, D., Hei, Y., Sun, H., Pan, T. and Ma, Z. (2025) Heparin and Dnase I Treat Myocardial Injury in Septic Mice. *Shock*, **63**, 908-918. <https://doi.org/10.1097/shk.0000000000002566>
- [58] Hu, C., Xuan, Y., Zhang, X., Liu, Y., Yang, S. and Yang, K. (2022) Immune Cell Metabolism and Metabolic Reprogramming. *Molecular Biology Reports*, **49**, 9783-9795. <https://doi.org/10.1007/s11033-022-07474-2>
- [59] An, Z., Hu, H., Wang, Q., Qiu, Y., Chu, J., Xia, Y., *et al.* (2026) Dietary Selenium Deficiency Activates the NLRP3 Inflammasome to Induce Gallbladder Pyroptosis by Regulating Glycolysis and Histone Lactylation through ROS/HIF-1 α Pathway. *The Journal of Nutritional Biochemistry*, **147**, Article ID: 110118. <https://doi.org/10.1016/j.jnutbio.2025.110118>
- [60] Yu, X., Hu, X., Wang, D., Cui, P., Zeng, M., Li, M., *et al.* (2025) Macrophage S1PR2 Drives Sepsis-Induced Immunosuppression by Exacerbating Mitochondrial Fragmentation. *American Journal of Respiratory Cell and Molecular Biology*, **72**,

-
- 615-626. <https://doi.org/10.1165/remb.2024-0161oc>
- [61] Liu, R., Wu, Z. and Yu, H. (2020) Effect of Different Treatments on Macrophage Differentiation in Chronic Obstructive Pulmonary Disease and Repeated Pulmonary Infection. *Saudi Journal of Biological Sciences*, **27**, 2076-2081. <https://doi.org/10.1016/j.sjbs.2020.05.038>
- [62] Zhao, H., Park, J., Wang, Y., Chou, Y., Li, L., Raines, L.N., *et al.* (2025) Cancer Suppresses Mitochondrial Chaperone Activity in Macrophages to Drive Immune Evasion. *Nature Immunology*, **26**, 2185-2200. <https://doi.org/10.1038/s41590-025-02324-2>
- [63] Sapudom, J., Karaman, S., Mohamed, W.K.E., Garcia-Sabaté, A., Quartey, B.C. and Teo, J.C.M. (2021) 3D *in Vitro* M2 Macrophage Model to Mimic Modulation of Tissue Repair. *NPJ Regenerative Medicine*, **6**, Article No. 83. <https://doi.org/10.1038/s41536-021-00193-5>
- [64] Xiao, Y., Yu, Y., Hu, L., Yang, Y., Yuan, Y., Zhang, W., *et al.* (2023) Matrine Alleviates Sepsis-Induced Myocardial Injury by Inhibiting Ferroptosis and Apoptosis. *Inflammation*, **46**, 1684-1696. <https://doi.org/10.1007/s10753-023-01833-2>
- [65] Si, X., Huang, Z. and Pan, Z. (2024) Clinical Effects of Dexmedetomidine on Patients with Sepsis and Myocardial Injury. *Medicine*, **103**, e40257. <https://doi.org/10.1097/md.00000000000040257>
- [66] Zhang, K. and Jagannath, C. (2025) Crosstalk between Metabolism and Epigenetics during Macrophage Polarization. *Epigenetics & Chromatin*, **18**, Article No. 16. <https://doi.org/10.1186/s13072-025-00575-9>
- [67] Sánchez-Tarjuelo, R. (2026) The Genetic Regulation of Immune Cells upon Activation. *Advanced Genetics*, **115**, 1-52.