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Hans汉斯

SIRT1在脓毒症器官保护作用中的研究进展

陈梦晓[1]，吴　刚[2*]，杜姗姗[1]，徐可欣[1]，刘洁玲[1]，王智琦[1]

[1]湖北医药学院口腔医学院，湖北　十堰
[2]十堰市人民医院(湖北医药学院附属人民医院)急诊科，湖北　十堰

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摘　要

脓毒症属于因宿主抗感染应答失控而诱发的致命性器官功能衰竭，其致死率较高，临床干预手段相对匮乏。沉默信息调节因子1 (SIRT1)是一种依赖于NAD$^+$的去乙酰化酶，它通过调控炎症、氧化应激、自噬及凋亡等过程，对脓毒症所诱发的多器官损伤起到关键性的保护作用。本文系统综述SIRT1在脓毒症所致肝、肾、心、肺、肠损伤中的最新研究进展。在肝脏，SIRT1激活AMPK信号通路促进自噬，减轻炎症与代谢应激；在肾脏，SIRT1上调PGC-1α改善线粒体功能，减少氧化应激和细胞凋亡；在心肌，SIRT1通过Nrf2/HO-1轴增强抗氧化防御，同时激活AMPK促进自噬；在肺脏，SIRT1可通过调节巨噬细胞的极化状态与线粒体自噬过程，减轻炎症反应及内皮细胞损伤。在肠道中，SIRT1被激活后能够抑制活性氧的生成，同时使紧密连接蛋白保持正常表达水平，进而推动肠道屏障功能恢复。这些结果提示，SIRT1经由多种信号途径展现出抗炎、抗氧化、抗凋亡及自噬调节等功能，可作为脓毒症所致器官损伤的潜在干预靶点，为该病的临床治疗提供了新的理论依据。

关键词

脓毒症，SIRT1，器官损伤，炎症，氧化应激，自噬

Research Progress on the Protective Role of SIRT1 in Sepsis-Induced Organ Injury

Mengxiao Chen[1], Gang Wu[2*], Shanshan Du[1], Kexin Xu[1], Jieling Liu[1], Zhiqi Wang[1]

[1]School of Stomatology, Hubei University of Medicine, Shiyan Hubei
[2]Department of Emergency Medicine, Shiyan People's Hospital (The Affiliated People's Hospital of Hubei University of Medicine), Shiyan Hubei

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[*]通讯作者。

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Abstract

Sepsis refers to a fatal organ dysfunction arising from an aberrant host response to infection, characterized by high mortality and limited treatment options. SIRT1 (silent information regulator 1) is an NAD$^+$-dependent deacetylase that confers significant protection against multi-organ damage induced by sepsis through modulation of inflammation, oxidative stress, autophagy, and apoptosis. This article systematically reviews recent progress on SIRT1 in sepsis-induced injuries of the liver, kidney, heart, lung, and intestine. In the liver, SIRT1 activates AMPK signaling to promote autophagy and alleviate inflammation and metabolic stress. In the kidney, SIRT1 upregulates PGC-1α to improve mitochondrial function and reduce oxidative stress and apoptosis. In the heart, SIRT1 enhances antioxidant defense via the Nrf2/HO-1 axis and activates AMPK to promote autophagy. In the lung, SIRT1 modulates macrophage polarization and mitophagy, thereby reducing inflammation and endothelial injury. In the intestine, SIRT1 activation suppresses reactive oxygen species production and maintains normal expression of tight junction proteins, thus promoting intestinal barrier repair. These findings indicate that SIRT1 exerts anti-inflammatory, antioxidant, anti-apoptotic, and autophagy-regulating effects through multiple pathways, positioning it as a potential therapeutic target for sepsis-induced organ damage and providing a new theoretical basis for clinical management.

Keywords

Sepsis, SIRT1, Organ Injury, Inflammation, Oxidative Stress, Autophagy

1. 引言

脓毒症系宿主对感染应答失调所致的一种致命性器官功能障碍，其全球发病与死亡率居高不下[1]。2020 年中国进行的横断面分析证实，重症监护病房(ICU)患者中脓毒症发病率可高达 20%，患者三个月内死亡率为 35.5% [2]。脓毒症不仅发病率和死亡率居高不下，治疗费用也相当高昂，因此长期以来一直是公共健康领域的重大威胁[3]。脓毒症不仅涉及全身性炎症或免疫失衡，还导致多器官功能改变。它的发病机理极为复杂，涵盖了多种病理生理过程，如炎症失调、免疫障碍、线粒体损伤、凝血障碍、自噬(resolution)等[4]。脓毒症常并发器官功能障碍，不仅可导致患者预后不佳，即便在出院后，仍可能出现多种长期后遗症，例如精神疾病、认知障碍及心血管疾病等，从而对全球健康与社会经济构成重大威胁[5]。然而，目前尚无特定治疗策略能够持续挽救败血症患者的生命[6]。

沉默信息调节因子 1 (Silent information regulator 1, SIRT1)属于 Sirtuins 蛋白家族，是一种高度保守的 NAD$^+$依赖性去乙酰化酶，其脱乙酰化反应需要 NAD$^+$作为共同底物。该酶介导的去乙酰化修饰在细胞衰老、凋亡、糖脂代谢、氧化应激及炎症反应等多个生物学过程中发挥关键调控作用[7] [8]。SIRT1 在脓毒症中的作用已被广泛研究，作为去乙酰化酶，SIRT1 调节炎症细胞的分泌，影响其分化、激活和成熟，同时高水平的 NAD$^+$可激活 SIRT1，进而抑制免疫细胞和内皮细胞的细胞凋亡和功能障碍，最终改善脓毒症的进展[9]。研究表明，SIRT1 能通过促进蛋白激酶 B (一种丝氨酸/苏氨酸激酶)的去乙酰化，抑制核转录因子-κB (Nuclear factor-kappa B, NF-κB)的激活，从而减少促炎细胞因子的产生并缓解巨噬细胞炎症。相

反，SIRT1 的缺失会导致蛋白激酶 B 过度乙酰化，加剧巨噬细胞的炎性细胞因子的产生，促进脓毒症进展[10] [11]。接下来本综述聚焦于 SIRT1 在脓毒症相关脏器损失中潜在调控机制及相关信号通路的最新进展，阐明 SIRT1 在脓毒症发病机制中的作用，并探索潜在的新型治疗策略。

2. SIRT1 在脓毒症脏器损伤中的保护作用

2.1. SIRT1 在脓毒症肝损伤中的保护作用

在人体解剖结构中，肝脏因其双重血供系统而具有显著的特殊性，其负责多种功能，包括细胞因子的产生、免疫活动的协调以及细菌清除，因此作为炎症和免疫控制的枢纽，它也是脓毒症侵袭下最易受损的器官之一，脓毒症引起的肝损伤死亡率可高达 68% [12]-[14]。脓毒症所致肝损伤的临床表现主要包括肝功能障碍、肝脏生化指标异常升高，以及肝衰竭风险[15]，肝损伤可以预测脓毒症患者的预后不佳[16]。然而，脓毒症所致肝损伤的病理机制较为复杂，涵盖了多个生物学过程与信号通路的共同参与，体现出多种致病因素之间相互协同、彼此影响的特征[2]。越来越多的证据表明，SIRT1 的激活能防止脓毒症引起的肝损伤，表明战略性靶向 SIRT1 是临床上脓毒症诱发肝损伤的合理治疗方法[17]。SIRT1 是 Sirtuins 家族中的重要成员，能够经由对自噬过程的调控，在肝脏代谢性损伤的防护中承担重要功能[18]，SIRT1 能通过与多个靶点相互作用，对其下游分子 AMP 依赖的蛋白激酶(AMP-dependent protein kinase, AMPK)的去乙酰化修饰进行调控。在能量匮乏或细胞应激条件下，磷酸化 AMPK (p-AMPK)水平上升，继而增强 SIRT1 的表达。这一过程可激活自噬通路，进而调节能量稳态和代谢应激以缓解脓毒症诱发肝损伤的炎症反应[19] [20]。

2.2. SIRT1 在脓毒症急性肾损伤中的保护作用

脓毒症引起的急性肾损伤(Sepsis-induced acute kidney injury, SA-AKI)是该病人群体中一种发生率高且病情危重的并发症，其特征为发病与死亡风险均处于较高水平[21] [22]，SA-AKl 的病理生理涉及微血管损伤，可能导致入球小动脉收缩和管内压力升高，导致肾小球过滤功能持续下降[23]。尽管 SA-AKI 的具体病理生理机制尚不完全明确，目前研究主要集中于炎症反应、补体系统激活、线粒体功能异常以及微循环障碍等方面[24]。现有研究已表明，SIRT1 能够经由多条信号途径对基因转录过程加以调控，进而发挥保护肾小管上皮细胞的作用：一方面减轻由氧化应激所诱导的细胞损伤，另一方面抑制肾脏局部的炎症反应；同时，SIRT1 还可改善线粒体功能状态，并降低肾小管细胞的凋亡水平[25] [26]。SIRT1 是关键的氧化应激抑制剂，在多种模型中对肾损伤具有保护作用[27]，氧化物酶体增殖物激活受体 γ 共激活剂 -1α (peroxisome proliferation-activated receptor-γ-coactivator 1α, PGC-1α)作为 SIRT1 下游的关键靶分子，能够调控线粒体的生物转化和代谢。在一项研究中[28]，右美托嘧啶预处理 SA-AKI 后，能增加 SIRT1 和 PGC-1α 的表达，从而减少氧化应激和细胞凋亡来改善 AKI。Chu 等人[29]的研究表明，SIRT1 经其特异性激活剂 SRT1720 激活后，可有效缓解小鼠 SA-AKI 模型中的炎症反应、氧化应激及线粒体功能障碍，进而起到保护肾功能的作用。这些发现证实了 SIRT1 在 SA-AKI 治疗中的作用，并为其多靶点疗效提供了机制框架。

2.3. SIRT1 在脓毒症心肌损伤中的保护作用

脓毒症引起的心肌功能障碍，称为脓毒症诱发心肌病或脓毒症诱发心肌损伤(Sepsis-induced myocardial injury, SIMI) [30]，脓毒症时的心肌损伤会加速脓毒症进展，是导致多器官功能障碍综合征和预后不良的重要因素[31]。临床研究表明，在脓毒症发展过程中，持续且过度的炎症反应会触发免疫细胞(包括中性粒细胞和巨噬细胞)的激活[32] [33]，细胞因子过度释放，以及补体系统激活，这些级联反应最终导

致免疫失调，表现为同时出现过度的炎症反应和免疫抑制，最终导致组织和器官损伤[34] [35]。研究证实，SIRT1 能促进核因子 E2 相关因子 2 (Nuclear factor E2-related factor 2, Nrf2)的活化过程，并诱导其向细胞核内易位，从而增强 Nrf2 的 DNA 结合活性及其转录功能，这一机制有助于防止氧化应激所诱发的组织氧化损伤及细胞凋亡[36]。Nrf2 表达升高可驱动血红素加氧酶-1 (Heme oxygenase-1, HO-1)水平上调，进而加速 NF-κB 抑制蛋白的降解，从而限制了 NF-κB 的激活并减轻了炎症反应[37]。因此，激活 SIRT1/Nrf2/HO-1 信号轴可增强抗氧化防御，抑制炎症与细胞凋亡，并维持细胞稳态，这表明其在 SIMI 中发挥关键保护作用[38]。SIRT1 也可通过活化 AMPK 促进自噬，从而保护缺氧引起的心肌损伤[39]。Wang 等人[40]在脓毒症心肌损伤模型中证明提高 SIRT1 水平能够抑制心肌细胞凋亡、缓解氧化应激状态、提升自噬活性，从而有效改善心功能异常。

2.4. SIRT1 在脓毒症急性肺损伤中的保护作用

脓毒症引发多器官功能障碍时，肺脏是最先受累且敏感性最高的靶器官[41]。在脓毒症诱发的急性肺损伤(sepsis-induced acute lung injury, S-ALI)患者中，患者由于肺部发生炎症反应并伴有组织结构破坏，气体交换能力随之下降[42] [43]。该疾病所涉及的病理机制主要包括：肺血管内皮细胞受损、肺泡表面活性物质功能减退致使表面张力异常、多种炎症因子的释放，以及肺间质出现纤维化改变。其临床特征为系统性炎症反应综合征，主要表现为持续性低氧血症及进行性呼吸困难[44] [45]。研究表明[46]，SIRT1 信号通路可通过缓解脓毒症所致急性肺损伤中的炎症反应，调控肺内多种细胞的功能。SIRT1 缺陷会导致 CLP 模型中的肺内皮损伤进一步恶化，同时使脓毒症病情更为严重，而恢复 SIRT1 活性可缓解 S-ALI 和脓毒症的严重程度。Ge 等人[47]的研究证实，汉黄芩苷能通过激活 SIRT1-叉头框蛋白 1 (Forkhead box class O 1, FOXO1)信号通路显著提高小鼠的存活率，有效抑制 M1 巨噬细胞极化，从而减轻了 ALI 引起的肺部病理损伤和炎症细胞浸润。

2.5. SIRT1 在脓毒症肠损伤中的保护作用

脓毒症的发生源于炎症反应与免疫抑制之间的稳态失衡[48]，进而诱发系统性炎症失控及免疫应答紊乱。在脓毒症病程中，肠道损伤主要表现为肠道屏障功能障碍，其特征包括微生物菌群失调、肠道通透性增加所致细菌易位增加，以及免疫反应抑制[49]。上述病理过程形成正反馈循环，进一步加剧肠道屏障损伤，并加速脓毒症从肠道向多个远隔器官的播散[50]。此外，肠道菌群紊乱可能引起肠道免疫细胞的异常激活，从而促使炎症因子表达水平升高。该过程可增加肠道通透性，促使细菌、细菌产物及其他肠腔内物质发生易位[51]。肠道菌群的动态平衡与组成因此受到破坏，使受损肠道中的细菌及毒素进入血液循环，引发多器官炎症与感染。这一系列变化可导致全身性炎症反应，成为脓毒症发病机制中的关键驱动因素[52] [53]。与此同时，脓毒症病程可加剧肠道中炎症因子的过度生成[54]。此外，在病原体清除过程中，中性粒细胞外陷阱的招募与激活与内质网应激诱导的活性氧生成同时发生，从而引起肠道屏障的氧化性损伤[55]。研究显示，激活 SIRT1/p62 信号通路可抑制氧化应激反应并改善肠道功能紊乱，从而减轻脓毒症的病理进程[56]。白藜芦醇作为已知活性最强的 Sirtuins 激活剂之一[57]，在脓毒症诱导的肠损伤小鼠模型中可显著上调 SIRT1 的表达。白藜芦醇通过调控 NADPH 氧化酶 1 (NADPH oxidase1, NOX1)/SIRT1 信号通路，可有效降低炎症细胞因子的分泌水平，激活自噬过程，阻断活性氧的产生，同时使紧密连接蛋白的表达维持在正常状态。这些效应共同促进了受损肠道屏障功能的重建，并减轻了肠组织损伤[58]。

2.6. SIRT1 在脓毒症中的前景与展望

综上所述，SIRT1 具有抗炎、抗氧化、抗凋亡、细胞保护作用，使其成为脓毒症潜在的治疗靶点。研

究人员已发现并开发出一系列 SIRT1 激动剂与拮抗剂，为未来研究提供了宝贵的见解与潜在方向[59]。为确保基于 SIRT1 的药物能够有效递送，可采用多种策略：(1) 使用单核巨噬细胞作为 SIRT1 药物的载体；(2) 利用靶向特定目标的纳米技术递送系统；(3) 施用 SIRT1 调节剂，如白藜芦醇和槲皮素；(4) 采用 miRNA 海绵技术，增强靶细胞或特定器官中 SIRT1 的表达。上述方法为开发基于 SIRT1 的治疗策略以干预脓毒症诱发的器官功能障碍提供了基础。尽管细胞和动物实验已取得显著进展，但目前对 SIRT1 调控脓毒症机制的理解仍不明确，现有研究多集中于 SIRT1 在单一靶器官中的作用，而关于 SIRT1 调节剂的临床试验数据极为匮乏，这限制了对 SIRT1 在脓毒症作用中的全面认识[60] [61]。为解决上述限制，未来研究应结合多学科方法及先进技术(如基因组学、蛋白质组学和代谢组学)深入探讨 SIRT1 在脓毒症中的机制，以全面阐明其作用[11] [62]。整合这些研究的发现，有望开发出更具特异性和有效性的 SIRT1 调节剂，为脓毒症的预防与治疗提供新策略。

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