Global Science Publishing

青蒿素酯通过LncRNA MALAT1/miR-155/Nrf2轴重塑巨噬细胞极化平衡缓解脓毒症肝损伤的研究进展

李玉红

浙江树人学院树兰国际医学院，树兰（杭州）医院手术麻醉科，浙江杭州

DOI:10.62836/medicine.v3i5.1552

摘要：脓毒症性肝损伤的核心免疫病理环节在于肝脏巨噬细胞*M*1/*M*2极化平衡的丧失。青蒿素酯作为青蒿素的重要衍生物，兼具抗炎与免疫调节潜能，但其肝保护效应的分子框架尚待系统阐释。长链非编码RNA MALAT1作为巨噬细胞可塑性的上游调控节点，将青蒿素酯的药理作用与ceRNA网络联系起来。本综述以MALAT1/PTBP1/IFIH1轴与miR-155/Nrf2轴为双轨线索，系统梳理青蒿素酯经MALAT1相关网络重塑巨噬细胞极化平衡的分子逻辑。现有证据提示，青蒿素酯下调MALAT1，既削弱PTBP1/IFIH1依赖的M1极化驱动，又通过调整miR-155对Nrf2的抑制强度，协同激活Nrf2/HO-1抗氧化轴，在净效应上推动巨噬细胞由M1向M2偏移。这一“源头抑M1、下游促M2”的整合模型，为青蒿素酯靶向肝脏免疫微环境的脓毒症辅助治疗定位提供了理论依据。

关键词：青蒿素酯；脓毒症；肝损伤；巨噬细胞极化；*LncRNA MALAT*1；*miR*-155；*Nrf*2

Research Progress on Artemisinin Esters Ameliorating Sepsis-Induced Liver Injury by Remodeling Macrophage Polarization Balance via the LncRNA MALAT1/MiR-155/Nrf2 Axis

Yuhong Li

Department of Anesthesiology, Shulan (Hangzhou) Hospital, Shulan International Medical College, Zhejiang Shuren University, Hangzhou, Zhejiang, China

Abstract: The core immunopathological feature of sepsis-induced liver injury lies in the loss of the M1/M2 macrophage polarization balance. Artemisinin esters, key derivatives of artemisinin, possess anti-inflammatory and immunomodulatory properties, yet the molecular framework underlying their hepatoprotective effects remains to be systematically elucidated. The long non-coding RNA MALAT1 serves as an upstream regulatory node of macrophage plasticity, bridging the pharmacological actions of artemisinin esters with ceRNA networks. Taking the MALAT1/PTBP1/IFIH1 axis and the miR-155/Nrf2 axis as dual tracks, this review systematically examines the molecular logic by which artemisinin esters remodel macrophage polarization balance through MALAT1-related networks. Current evidence suggests that artemisinin esters downregulate MALAT1, thereby attenuating PTBP1/

**基金项目：浙江省中医药科技计划项目（2023ZL593）

通讯作者：李玉红

IFIH1-dependent M1 polarization while modulating miR-155-mediated repression of Nrf2, and synergistically activating the Nrf2/HO-1 antioxidant axis, ultimately shifting macrophages from M1 toward M2. This integrative “upstream M1 suppression and downstream M2 promotion” model provides a theoretical basis for positioning artemisinin esters as adjunctive therapeutics for sepsis targeting the hepatic immune microenvironment.

Keywords: artemisinin esters; sepsis; liver injury; macrophage polarization; LncRNA MALAT1; miR-155; Nrf2

脓毒症是宿主对感染反应失调所致的危及生命的器官功能障碍[1]。全球疾病负担研究估计，2017年全球脓毒症新发病例约4890万，相关死亡约1100万，占全部全球死亡的19.7%[2]。肝脏作为免疫与代谢的核心枢纽，在脓毒症早期即可受累，脓毒症性肝损伤不仅是多器官功能障碍综合征的重要组分，也与患者不良预后密切相关[3]。近年来的免疫代谢进展揭示，肝脏巨噬细胞，尤其是定居于肝窦的Kupffer cell（库普弗细胞）及募集的单核来源巨噬细胞，其表型可塑性是决定损伤走向修复或恶化的核心枢纽[4]。然而，针对巨噬细胞极化的靶向干预手段仍十分有限。青蒿素酯作为青蒿素的重要衍生物，除抗疟活性外，已被证实具有抗炎与免疫调节潜能，在脓毒症相关器官保护中展现出独特价值[5,6]。尤为关键的是，新近研究将长链非编码RNA MALAT1推向了调控巨噬细胞可塑性的前沿[7]。本综述以MALAT1/PTBP1/IFIH1轴与miR-155/Nrf2轴为双轨线索，探讨青蒿素酯经MALAT1相关网络重塑巨噬细胞极化平衡的潜在分子逻辑。

1 脓毒症性肝损伤中的巨噬细胞极化失衡

脓毒症诱导的肝损伤并非单纯由病原体直接毒性所致，而主要是免疫失调驱动的炎症性损伤。肠道来源的脂多糖经门静脉入肝，被Kupffer cell及募集巨噬细胞表面的Toll样受体4识别，迅速激活NF-κB等促炎级联[8]。单细胞转录组研究显示，脓毒症肝脏中巨噬细胞被大量募集并活化，部分参与免疫稳态的重建，但其高表达的Tnf、Il1b、Il6等转录本同时驱动了肝脏炎症风暴[9,10]。在这一阶段，巨噬细胞主要呈现经典活化的M1表型，代谢特征以糖酵解为主，并伴随大量活性氧生成，在清除病原体的同时加剧肝细胞损伤[11,12]。与M1型相对，替代活化的M2型巨噬细胞依赖氧化磷酸化供能，通过IL-10、Arg-1等介质抑制炎症、促进修复[13]。在持续性脓毒症刺激下，M1型持续占优势而M2型极化不足或功能受抑，炎症无法消退、肝细胞死亡持续存在，并启动纤维化程序[14]。因此，将巨噬细胞从M1主导的促炎状态重编程为M2主导的修复状态，是脓毒症肝损伤极具前景的干预策略[4]。

2 LncRNA MALAT1：ceRNA机制与巨噬细胞可塑性的交汇节点

MALAT1是一个在进化上高度保守的核内长链非编码RNA[15]。免疫学研究揭示，其在脓毒症等炎症状态下于巨噬细胞中显著上调，并作为表观调控节点驱动M1极化[16]。机制上，MALAT1可作为竞争性内源RNA（ceRNA）发挥作用；但值得注意的是，在巨噬细胞中，MALAT1的促M1效应并不完全依赖经典的miRNA“海绵”功能。Yang等[17]的研究表明，MALAT1通过招募RNA结合蛋白PTBP1促进IFIH1（MDA5）的表达，进而经IRF1/STAT1通路驱动M1型极化；青蒿琥酯正是通过下调MALAT1来抑制这一蛋白–RNA互作依赖的促炎回路。这构成了青蒿素酯作用于巨噬细胞的上游“蛋白依赖”分支。

与此同时，ceRNA网络构成了MALAT1调控的另一条可能分支。在巨噬细胞极化调控中，miR-155被公认为促M1 miRNA，而MALAT1与miR-155之

间存在调控关联[18]。更为关键的是，miR-155被证实可靶向抑制Nrf2的表达：在LINC00240/miR-155/Nrf2轴的研究中，miR-155的抑制导致Nrf2表达升高，并伴随M2巨噬细胞极化增强[19,20]。由此，“MALAT1 → miR-155 → Nrf2”的ceRNA逻辑得以成立。需要指出的是，该轴在脓毒症肝损伤巨噬细胞中的直接因果证据尚不充分，但它为理解青蒿素酯下调MALAT1后如何“顺势”解除对Nrf2的转录后抑制、进而促进M2偏移，提供了一个机制上自洽的假说框架。两条分支的并置

“PTBP1/IFIH1依赖的M1驱动抑制与miR-155/Nrf2依赖的M2许可”共同构成了青蒿素酯调控巨噬细胞极化的双轨模型。

3 青蒿素酯的药理学基础与Nrf2/HO-1通路的极化调控功能

青蒿素酯是青蒿素的酯类衍生物，其过氧桥结构既是抗疟活性的基础，也被证实参与Nrf2/ARE通路的激活[21]。在多种肝损伤模型中，青蒿琥酯的肝保护作用与其抑制NF-κB、同时解除NF-κB对Nrf2的转录抑制密切相关：NF-κB信号的下调伴随Nrf2蛋白水平升高及下游HO-1、NQO1的表达上调[22,23]。这一NF-κB/Nrf2的负向交叉对话，为青蒿素酯在脓毒症肝损伤中“抗炎”与“抗氧化”效应的耦合提供了药理学解释。

Nrf2/HO-1通路本身是连接氧化应激与巨噬细胞极化的核心枢纽。Nrf2的激活能够抑制M1极化并促进M2极化，其机制涉及HO-1的表达以及Nrf2对NF-κB的负向调控，并可能与TGF-β/SMAD、TLR/NF-κB及JAK/STAT等通路的交叉对话有关[24,25]。在脓毒症肝损伤的语境下，这一通路的意义尤为突出：M1极化伴随的糖酵解和活性氧爆发，恰恰是Nrf2激活所要拮抗的氧化还原状态；而Nrf2驱动的抗氧化程序则为依赖氧化磷酸化的M2表型创造了有利的胞内环境。因此，青蒿素酯对Nrf2/HO-1轴的直接激活，与其通过MALAT1下调对M1极化的上游抑制，在功能上形成了汇聚：前者从“下游”松动M1极化的氧化还原锁定，后者从“上游”削弱M1极化的转录驱动，二者共同增加了巨噬细胞向M2表型偏移的概率。

4 从M1抑制到M2促进的整合模型与转化挑战

综合现有证据，青蒿素酯缓解脓毒症肝损伤的巨噬细胞极化调控并非单一线性通路，而是一个“源头抑M1、下游促M2”的整合网络。在上游，青蒿素酯下调MALAT1，削弱PTBP1/IFIH1/STAT1轴对M1极化的驱动，并可能通过ceRNA机制调整miR-155对Nrf2的抑制强度。在下游，青蒿素酯激活Nrf2/HO-1抗氧化程序，缓冲M1相关的氧化应激，并通过代谢微环境的改善促进M2表型的稳定。这一双重作用最终将肝脏巨噬细胞池从促炎/损伤表型向抗炎/修复表型推移，打破“炎症–氧化应激”恶性循环。

然而，这一模型向临床转化的路径仍面临若干关键瓶颈。首先，现有证据几乎全部来源于LPS或盲肠结扎穿孔诱导的啮齿类模型，脓毒症的病因异质性与人类巨噬细胞亚群组成的差异限制了直接外推[26,27]。其次，MALAT1/miR-155/Nrf2轴中miR-155的中介必要性尚未在巨噬细胞特异性敲除或拯救实验中得以严格检验；已确立的PTBP1/IFIH1分支提示，MALAT1的促M1效应可能以蛋白–RNA互作为主，ceRNA机制可能处于辅助或情境依赖的地位[28]。这要求未来研究在明确miR-155功能贡献的同时，平行评估蛋白–RNA互作与ceRNA网络在巨噬细胞极化中的相对权重。此外，青蒿素酯的肝脏巨噬细胞靶向性不足、全身暴露可能带来的脱靶效应，也是实现精准免疫调节必须克服的药理学障碍。未来工作应优先利用髓系特异性基因编辑小鼠结合单细胞多组学，在在体水平解构MALAT1下游的因果网络，并探索基于巨噬细胞表面标志物的靶向递送策略[29,30]。

5 结论

脓毒症肝损伤的核心免疫病理环节在于巨噬细胞M1/M2极化平衡的丧失。LncRNA MALAT1作为巨噬细胞可塑性的上游调控节点，为理解青蒿素酯的肝保护机制提供了新的分子框架。现有证

据支持青蒿素酯通过下调MALAT1，经由PTBP1/IFIH1依赖的M1驱动抑制，并协同Nrf2/HO-1抗氧化轴的激活，在净效应上推动巨噬细胞由M1向M2偏移。miR-155/Nrf2 ceRNA分支在当前证据链中更多扮演“机制上合理但因果待验”的角色，但其与PTBP1/IFIH1分支的并置，恰恰勾勒出青蒿素酯调控巨噬细胞可塑性时“蛋白互作与RNA网络交织”的复杂图景。未来研究若能在巨噬细胞特异性遗传模型中厘清两条分支的相对贡献，将为青蒿素酯作为靶向肝脏免疫微环境的脓毒症辅助治疗药物提供更为坚实的理论基础。

参考文献

[1] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[J]. JAMA, 2016, 315(8): 801-810.

[2] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study[J]. Lancet, 2020, 395(10219): 200-211.

[3] Ni L, Chen D, Zhao Y, et al. Unveiling the flames: macrophage pyroptosis and its crucial role in liver diseases. Front Immunol. 2024, 15: 1338125.

[4] Wang C, Ma C, Gong L, et al. Macrophage polarization and its role in liver disease[J]. Front Immunol, 2021, 12: 803037.

[5] 李同钦,董小荣,吕雅婷,等.青蒿琥酯治疗脓毒症的作用机制研究进展[J].2026,41(4):1146-1152.

[6] Zhao X, Huang X, Yang C, et al. Artemisinin Attenuates Amyloid-Induced Brain Inflammation and Memory Impairments by Modulating TLR4/NF-κB Signaling. Int J Mol Sci. 2022, 23(11): 6354.

[7] Jiang M, Lv Z, Huang Y, et al. Quercetin Alleviates Lipopolysaccharide-Induced Inflammatory Response in Bovine Mammary Epithelial Cells by Suppressing TLR4/NF-κB Signaling Pathway. Front Vet Sci. 2022, 9: 915726.

[8] Mountford S, Effenberger M, Noll-Puchta H, et al. Modulation of Liver Inflammation and Fibrosis by Interleukin-37. Front Immunol. 2021, 12: 603649.

[9] Zhou C. A multitherapy single-cell atlas reveals cell type-specific modulation in sepsis-induced liver injury. J Immunol. 2026, 215(2): vkaf351.

[10] Zhang Q, Liu J, Shen J, et al. Single-cell RNA sequencing reveals the effects of capsaicin in the treatment of sepsis-induced liver injury. MedComm (2020). 2023, 4(5): e395.

[11] Ji Y, Li X, Yao X, et al. Macrophage polarization: molecular mechanisms, disease implications, and targeted therapeutic strategies. Front Immunol. 2025, 16: 1732718.

[12] Guo Z, Wang L, Liu H, et al. Innate Immune Memory in Monocytes and Macrophages: The Potential Therapeutic Strategies for Atherosclerosis. Cells. 2022, 11(24): 4072.

[13] Chen Y, Yang L, Li X. Advances in Mesenchymal stem cells regulating macrophage polarization and treatment of sepsis-induced liver injury. Front. Immunol. 14: 1238972.

[14] 何泽英,朱宏泉.巨噬细胞极化在脓毒症及脓毒症相关肝损伤的作用[J].医学理论与实践,2024,37(22):3814-3816.

[15] Zhao Q, Pang G, Yang L, et al. Long Noncoding RNAs Regulate the Inflammatory Responses of Macrophages. Cells. 2022, 11(1): 5.

[16] Arun G, Aggarwal D, Spector DL. MALAT1 Long Non-Coding RNA: Functional Implications. Noncoding RNA. 2020, 6(2): 22.

[17] Yang Z, Xia H, Lai J, et al. Artesunate alleviates sepsis-induced liver injury by regulating macrophage polarization via the lncRNA MALAT1/PTBP1/IFIH1 axis.Diagnostic Microbiology and Infectious Disease, 2024, 110(1): 10.

[18] Yuan Z, Huang Y, Sadikot RT. Long Noncoding RNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 Promotes HIV-1 Replication through Modulating microRNAs in Macrophages. J Virol. 2023, 97(6): e0005323.

[19] Wu H Y, Liu K, Zhang J L. LINC00240/miR-155 axis regulates function of trophoblasts and M2 macrophage polarization via modulating oxidative stress-induced pyroptosis in preeclampsia. Molecular medicine (Cambridge, Mass.), 2022, 28(1): 119.

[20] Yang ZB, Chen WW, Chen HP, et al. MiR-155 aggravated septic liver injury by oxidative stress-mediated ER stress and mitochondrial dysfunction via targeting Nrf-2. Exp Mol Pathol. 2018, 105(3): 387-394.

[21] Wei M, He J, Zhang Y, et al. Artesunate Targets MBL2 to Modulate the TLR4/NRF2/HO-1 Axis and Ameliorate Podophyllotoxin-Induced Liver Injury. Drug Des Devel Ther. 2026, 20: 608177.

[22] Kuang L, Zhang C, Li B, et al. Human Keratinocyte-Derived Exosomal MALAT1 Promotes Diabetic Wound Healing by Upregulating MFGE8 via microRNA-1914-3p. International Journal of Nanomedicine. 2023, 18: 949-970.

[23] 张晓勇,周春祥.青蒿琥酯对大鼠肝Kupffer细胞分泌肝纤维化相关细胞因子的影响[J].安徽医学,2014,35(10):1437-1439.

[24] Wang L, He C. Nrf2-mediated anti-inflammatory polarization of macrophages as therapeutic targets for osteoarthritis.Front Immunol. 2022, 13: 967193.

[25] Liu Y, Zhang M, Wang T, et al. Reactive Oxygen Species in Asthma: Regulators of Macrophage Polarization and Therapeutic Implications: A Narrative Review. J Asthma Allergy. 2025, 18: 1129-1146.

[26] Chen JW, Liu CY, Li S, et al. Sepsis-associated liver injury: Mechanisms and potential therapeutic targets. World J Gastroenterol. 2024 Nov 14; 30(42): 4518-4522.

[27] 冯禹涵,陈金子,倪嘉威,等.脓毒症相关肝损伤的发病机制及治疗研究进展.国际麻醉学与复苏杂志,2026,47(8):728-734.

[28] Li B, Yu M, Pan X, et al. Artesunate reduces serum lipopolysaccharide in cecal ligation/puncture mice via enhanced LPS internalization by macrophages through increased mRNA expression of scavenger receptors. Int J Mol Sci. 2014, 15(1): 1143-61.

[29] 程志杰,左瑞静,李欢欢,等.脓毒血症患者巨噬细胞外泌体miR-155对内皮细胞铁死亡的干预机制[J].昆明医科大学学报,2026,47(2):83-92.DOI:10.12259/j.issn.2095-610X.S20260209.

[30] Xie W, Lv L, Wang T, et al. The efficacy of artesunate in animal models of sepsis: a systematic review and meta-analysis. Front Pharmacol. 2026, 17: 1748083.

Copyright © 2026 by author(s) and Global Science Publishing 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