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系统性炎症反应介导慢加急性肝衰竭的研究进展

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摘　要

慢加急性肝衰竭(ACLF)指慢性肝病急剧恶化并出现功能障碍，是一种伴有肝内外器官衰竭、短期预后不佳的严重临床综合征。虽然目前发病机制尚未完全阐明，但可以明确系统性炎症反应与ACLF的起病和进展具有密切的关联。细菌感染、过量的酒精摄入以及嗜肝病毒活动可以释放病原相关分子模式和/或损伤相关分子模式激活炎症反应，损害重要脏器功能，诱导ACLF发生。疾病晚期由于炎症反应持续存在，先天性免疫细胞功能受抑难以抵御再发感染，病死率进一步升高。同时反应产生的炎性介质还将阻碍肝脏修复、改变血流动力学及线粒体功能加剧器官损伤。白介素22、间充质干细胞等新现的治疗方式可以改善炎症反应、降低感染风险、延缓病情进展，为部分患者后续接受肝移植治疗争取更多时间。针对系统性炎症作用于ACLF的诸多环节还有待进一步研究，开发更加有效的抗炎治疗手段也将提高患者生存率并缓解疾病负担。

关键词

慢加急性肝衰竭，系统性炎症反应，免疫抑制，器官衰竭

Advances in Research on the Role of Systemic Inflammatory in Mediating Acute-on-Chronic Liver Failure

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Abstract

Acute-on-chronic liver failure (ACLF) is delineated as a rapid exacerbation of chronic hepatic disorders, culminating in functional impairment and is identified as a grave clinical syndrome characterized by both hepatic and extrahepatic organ failures, concomitant with a dismal short-term prognosis. The pathogenesis of ACLF, albeit not entirely elucidated, has been unequivocally associated with systemic inflammatory playing a pivotal role in its initiation and progression. The release of pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) triggered by bacterial infections, excessive alcohol consumption, and active hepatotropic viral infections activates inflammatory responses. This, in turn, inflicts damage upon major organs function, precipitating the onset of ACLF. In the advanced stages of the disease, the protracted presence of inflammatory responses leads to a suppression of innate immune cell functions, thereby impairing the host's defense against recurrent infections and further escalating mortality rates. Concurrently, the inflammatory mediators impede hepatic regeneration, modify hemodynamics, and deteriorate mitochondrial function, thus exacerbating organ damage. Emerging therapeutic interventions, such as the administration of interleukin-22 and the employment of mesenchymal stem cells, have shown promise in ameliorating the inflammatory response, diminishing infection risks, and retarding disease progression, thereby extending the temporal window for potential liver transplantation in a subset of patients. The intricate involvement of systemic inflammation in the multifaceted progression of ACLF necessitates further investigation, with the aim of developing more efficacious anti-inflammatory therapeutic modalities to enhance patient survival rates and alleviate disease burden.

Keywords

Acute-on-Chronic Liver Failure, Systemic Inflammatory, Immunosuppression, Organ Failure

1. 引言

慢加急性肝衰竭(Acute-on-chronic liver failure, ACLF)这一概念于 1995 年首次提出[1]，用来描述持续性慢性肝病和急性肝损伤同时存在的情况，临床上主要表现为进行性加深的黄疸、严重的凝血功能障碍、乏力、纳差等症状，短时间内可以出现感染、腹水、胃肠道出血或肝性脑病等并发症，严重威胁患者的生命健康。ACLF 的发生常与促炎事件相关(如败血症、酒精性肝炎、病毒性肝炎等)，且与非 ACLF 患者相比系统性炎症反应(Systemic inflammation, SI)也更为严重，表现为白细胞计数和 C 反应蛋白水平明显升高[2]。炎症反应激活后释放大量的可溶性炎性介质，包括多种细胞因子、趋化因子、细胞外基质蛋白、生长因子，这些炎性介质直接介导组织损伤的同时还作用于免疫系统，促使免疫细胞活化、募集并产生效应分子加剧组织破坏。最终，过度的炎症反应将导致单个或多个器官功能障碍[3]，这也是 ACLF 的重要特征之一。本文就 SI 对 ACLF 发生与发展的影响进行综述，旨在开发炎症反应中的效应细胞或效应分子在 ACLF 靶向治疗中的应用。

2. 系统性炎症反应的发生机制

2.1. 触发因素

败血症引发的 ACLF 可以定义为细菌感染所致的免疫代谢失调和器官功能障碍，超过 30%的患者具有这种表现，是最为多见的诱发因素[2]。研究表明，革兰氏阴性菌细胞壁产生的脂多糖(Lipopolysaccharide, LPS)可以通过激活 Toll 样受体(Toll-like receptors, TLRs)和 NOD 样受体(NOD-like receptors, NLRs)信号通路诱发炎症反应。一方面，LPS 与 TLR4 结合后作用于下游的髓样分化因子 88(Myeloid differentiation factor 88, MyD88)，诱导肿瘤坏死因子 α (Tumour necrosis factor α, TNF-α)、白介素-6(Interleukin 6, IL-6)、IL-1β 等促炎细胞因子释放[4]。另一方面，LPS 可以被细胞质中的半胱天冬酶 4 和 5 识别，进而活化 NLR 并上调 IL-1β 和 IL-18 的表达[5] [6]。一项利用盲肠结扎穿刺法诱导败血症相关 ACLF 小鼠模型的研究还发现内皮细胞功能障碍可以激活肝细胞生长因子(Hepatocyte growth factor, HGF)-CCAAT 增强子结合蛋白 β (CCAAT-enhancer binding protein β, C/EBPβ)信号通路从而导致 ACLF [7]。该作用具体表现为：血管生成素 1 与血管生成素 2 比值减低使抗炎与促炎失衡，内皮细胞释放更多 HGF，高表达转录因子 C/EBPβ，最终肝细胞分化基因被抑制而发展成肝衰竭。

研究表明酒精过量仍是西方国家发生 ACLF 的重要诱因，尽管内在机制仍需进一步明确[2]。酒精的肝毒性主要体现在诱导炎症和促进细胞死亡两个方面，最终导致原有肝细胞功能受损和再生障碍。长期饮酒可以改变肠道菌群的构成，还可以直接影响肠黏膜屏障的完整性和通透性，进入循环的肠道菌群同样通过释放 LPS 作用于肝巨噬细胞并诱导炎症[8] [9]。然而，不同的诱因产生的炎症因子谱略有不同，酒精滥用的患者以 IL-8 升高为主，细菌感染的患者则以 IL-6 升高为主[10]。乙醇代谢过程中还产生大量活性氧(Reactive oxygen species, ROS)，可以使线粒体受损并诱导依赖内质网的凋亡程序启动[11]。还有研究表明，在酒精性肝炎患者中观察到肝再生相关的细胞因子缺乏，再生障碍在一定程度上解释了这类患者肝衰竭发生的机制[12]。

高达 38%的慢性乙型肝炎(Chronic hepatitis B, CHB)患者可因乙型肝炎病毒(Hepatitis B virus, HBV)再激活导致 ACLF [13]。通过转录组测序分析可以观察到，对比 CHB 患者、肝硬化患者及正常对照组，HBV-ACLF 患者的上调基因多与炎症反应和趋化反应相关[14]。此外，通过下调圆柱瘤病基因解除其对巨噬细胞中核转录因子 κB (Nuclear factor kappa-B, NF-κB)的抑制作用，可以增加 CC 趋化因子 2 (CC chemokine 2, CCL2)、CCL5、CCL20、CXC 趋化因子 5 (CXC chemokine 5, CXCL5)、CXCL6、CXCL8 (又称为 IL-8)、IL-6、IL-1β 表达，进而增强炎症细胞的趋化聚集，这也进一步证实了 HBV-ACLF 的炎症损伤机制。其中，IL-6、IL-8 不仅参与诱导急性炎症反应，还与 HBV-ACLF 不良预后相关联[15] [16]。

2.2. 激活途径

病原体相关分子模式(Pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(Damage-associated molecular patterns, DAMPs)是诱发 SI 的重要作用分子[17] [18]，病原菌和坏死细胞可以通过产生相应的效应分子触发细胞炎症因子释放，参与机体炎症反应介导的 ACLF。

当机体发生感染后，模式识别受体(Pattern-recognition receptors, PRRs)通过特有的结构域结合微生物表达的 PAMPs，驱动细胞内信号级联反应，进而引发炎症因子风暴[19]。前文提到的 LPS 可被 TLR4 识别就是通过 PAMP-PRR 模式结合[20]。肠道菌群的过度生长、肠黏膜通透性增加以及肠道先天性免疫功能障碍使细菌及其副产物由肠腔转移至肠系膜淋巴结和肠道相关的淋巴组织，细菌移位会导致体循环中高水平的 PAMPs 和持续性全身炎症反应[21] [22] [23]。此外，感染后产生的细菌毒力因子也能促进炎症反应[24]。不同于 PAMPs 的结构特征性识别，毒力因子主要通过功能特征性识别诱导炎症，并不依赖于 PRRs 存在。

DAMPs 主要在无菌性炎症中发挥作用，来源于坏死或受损的宿主细胞。当肝细胞发生坏死后细胞膜及细胞器膜破裂，使位于细胞核、线粒体和细胞质中的 DAMPs，如高迁移率族蛋白 1 (High mobility group box 1, HMGB1)、组蛋白、线粒体脱氧核糖核酸(Mitochondrial deoxyribonucleic acid, mtDNA)、甲酰基肽、三磷酸腺苷(Adenosine triphosphate, ATP)释放到细胞外基质[25]。DAMPs 与 PAMPs 发挥致炎作用的途径相似，在肝脏缺血-再灌注损伤模型中 HMGB1 可被晚期糖基化终末产物受体(Advanced glycosylation end product-specific receptor, RAGE)及 TLRs 识别并介导后续的炎症反应[26]。凋亡、焦亡、铁死亡等其它细胞死亡类型也能促进 DAMPs 的释放，并通过与特殊的 PRRs 结合作用于肝病患者的全身炎症反应[27]。

2.3. 免疫系统在炎症反应中的作用

急性失代偿(Acute decompensation, AD)相关的 SI 可以同时激活先天性免疫系统和获得性免疫系统，其中先天性免疫与 AD 向 ACLF 转化的关联更为密切[28]。ACLF 病理过程中产生多种细胞因子，共同作用诱导炎症反应激活免疫细胞进而调节免疫功能，其中常见的促炎因子有：TNF-α、IL-1β、IL-6，常见的抗炎因子有：IL-10、IL-4、IL-1 受体拮抗剂[29]。随着 ACLF 的病情进展还会出现免疫耐受，虽然这在一定程度上减轻了机体的炎症反应，但同时也增加了感染及器官衰竭的风险[30]，单核细胞、巨噬细胞、中性粒细胞等免疫细胞的表型变化和功能异常在免疫抑制过程中起到重要作用。

ACLF 早期单核细胞受趋化因子影响向感染部位聚集，通过人类白细胞抗原II类分子(Human leukocyte antigen-II, HLA-II)识别抗原，高表达 TLR-4，产生以 IL-1β、TNF-α、IL-12p70 为主的促炎因子及少量抗炎因子 IL-10，从而发挥促炎作用[31]。但在 ACLF 晚期则观察到 $CD14^+$ $HLA\text{-}DR^-$单核细胞样髓源抑制细胞(Mononuclear $CD14^+$ $HLA\text{-}DR^-$ myeloid-derived suppressor cells, M-MDSCs)明显增多[32]。M-MDSCs 能够抑制 T 淋巴细胞激活，减少 TLR 介导的促炎因子的释放以及削弱机体对细菌的吞噬作用，使机体更易受到再发感染打击，与不良预后密切相关。此外，Mer 受体酪氨酸激酶(Mer receptor tyrosine kinase, MERTK)高表达也能负性调节免疫反应，阻止单核细胞中 TLRs 激活，并且体外实验中还可以观察到 LPS 相关的促炎反应受 MERTK 过表达影响而减弱[33]。

巨噬细胞存在于大多数组织中，以肝脏内的 Kupffer 细胞最为多见(占总巨噬细胞的 80%)，参与肝脏的炎症、损伤、修复、纤维化及肿瘤发生的多个病理过程[34]。有研究发现不同的微环境信号(包括微生物代谢产物、活化的淋巴细胞和受损细胞及其产物)可以影响巨噬细胞分化，使其表现为 M1 型(经典活化型)或 M2 型(选择活化型)，其中前者可以释放大量促炎因子，后者则表现出抗炎、促进肝细胞再生的功能[35]。根据欧洲肝脏研究协会——慢性肝衰竭学会的分级标准，ACLF 分级越高，来源于 M2 表型的可溶性 CD163 释放就越多，提示患者预后越差[36]。巨噬细胞胞浆内的可变铁池(Labile iron pool, LIP)也参与肝细胞氧化应激损伤，相较于 ACLF 生存组，死亡组 LIP 含量明显升高[37]。

中性粒细胞也是感染早期募集的免疫细胞之一，具有清除病原体、使感染局限化的作用，但在反应过程中也不免损伤组织[38]。酒精性肝炎相关 ACLF 患者高表达趋化因子受体 CXCR1/2 的 CD11b + CD16 + 中性粒细胞受 IL-8 趋化作用影响向肝脏迁移，促进肝细胞坏死、凋亡，并且这种促细胞死亡作用可以被 CXCR1/2 拮抗剂 SCH527123 阻断[39] [40] [41]。活化的中性粒细胞可以释放大量的 ROS 发挥杀菌作用，但在 ACLF 晚期由于磷脂酶 C 活性减低、磷酸化不足将导致 ROS 生成不足、杀菌活性降低，产生免疫抑制[42] [43]。

3. 系统性炎症反应与 ACLF 的关系

3.1. 炎症反应对肝脏的影响

星状细胞具有储存维生素 A、调节肝窦血流、维持肝细胞表型及构建细胞外基质的作用，与肝脏稳态

密切相关[44]。SI 可以激活星状细胞，一方面通过活化巨噬细胞和粒细胞集落刺激因子(Granulocyte colony-stimulating factor, G-CSF)提高中性粒细胞活性，加剧肝细胞损伤；另一方面影响肝细胞再生[45] [46]。此外，通过组织学病理检查可以发现 ACLF 患者肝组织细胞水肿、脂肪变性、胆管性胆汁淤积、胆管炎明显高于慢性肝衰竭患者，其中胆汁性胆管淤积与 SI 密切相关，并且可以作为 ACLF 预后的独立预测因素[47]。

3.2. 炎症反应介导多器官功能障碍

器官衰竭的种类和数量与 ACLF 不良预后密切相关，死亡患者中大脑、循环、呼吸功能不全占比高达 95% [46]，并且当衰竭器官数目增多时死亡率也明显上升，例如出现两种器官衰竭时 28 天死亡率约为 32%，当出现三种及以上器官衰竭时死亡率将上升至 76.7% [2]。

SI 可能通过炎症反应促进细胞坏死凋亡、导致血流动力学紊乱以及改变能量代谢方式介导器官衰竭[48]。首先，PAMPs、G-CSF 能够刺激中性粒细胞生成并通过释放 ROS 和水解酶促进肝细胞死亡[28]。肝硬化组织中，LPS 诱导 NF-κB 依赖性的抗凋亡蛋白生成减少、未折叠蛋白反应激活，使肝细胞对凋亡信号更敏感[49]。其次，PAMPs、TNF-α 作用于血管内皮细胞释放大量一氧化氮(Nitric oxide, NO)，舒张全身血管使循环血量不足，通过负反馈调节肾血管收缩、灌注不足出现急性肾损伤，同时炎症反应中组织因子释放引起微血栓形成也会导致器官缺血缺氧[17]。最后，炎症反应期间急性期蛋白合成增多，能量需求增加，为了适应激增的能量需求，维持免疫反应活化状态，线粒体呼吸功能及外周器官氧化磷酸化过程被静默，心、肾功能急剧下降[50]。

4. 改善系统性炎症的治疗策略

SI 的严重程度与 ACLF 的预后密切相关[28]，即全身炎性反应越强，导致器官衰竭数目越多，患者短期内死亡风险越高，因此有效控制 SI 在 ACLF 的治疗中显得尤为重要。

人血白蛋白(Human serum albumin, HSA)能够通过扩容作用改善循环障碍和有效动脉血容量不足，还可以结合并灭活多种促炎分子，例如 PAMPs、前列腺素、NO、ROS，减轻炎性反应[51] [52] [53]。对于 ACLF 合并腹水的患者，反应诱导下 HSA、速尿、血管加压素联合输注治疗可以改善门脉高压所致的肠管充血水肿、肠道通透性增加，进而减轻肠道菌群移位、内毒素释放入血诱导的炎性反应[54]。急性失代偿性肝硬化合并自发性腹膜炎(Spontaneous bacterial peritonitis, SBP)患者预防性应用 HSA 已被证实能够降低肝肾综合征的患病率[55]，且对比仅使用抗生素治疗的肝硬化合并非 SBP 的细菌感染患者，加用 HAS 辅助治疗可以有效降低再发感染风险[56]。还有研究表明，HSA 透析联合肾脏替代治疗或人工肝支持治疗可以有效提高 ACLF 患者生存率[57] [58]。

IL-22 可以通过诱导肝细胞抗凋亡相关基因表达促进肝脏修复且能发挥抗菌作用，因而具有治疗 ACLF 的潜力。在四氯化碳介导的 ACLF 小鼠模型中可以观察到 IL-22Fc 能够逆转干扰素相关的抗再生通路 STAT1 与 IL-6 相关的促再生通路 STAT3 的比例失衡，还能通过 B 细胞淋巴瘤因子 2 (B-cell lymphoma factor, BCL)上调抗菌基因表达以达到促进肝再生、减轻感染的目的[59]。对于酒精性肝炎患者，应用 IL-22 治疗可以有效改善肝脏炎症、减少细菌感染[60]。

此外，TLR-4 拮抗剂 TAK-242 可以降低 LPS 相关的细胞因子释放和细胞死亡，减少器官损害[61]。细胞治疗也可用于 ACLF，移植人脐带间充质干细胞(Human umbilical cordderived mesenchymal stem cells, hUC-MSCs)后，ACLF 小鼠肝组织中炎性细胞浸润减少、促炎因子水平降低，肝功能、肝纤维化都有明显改善[62]。

5. 总结与展望

ACLF 持续性 SI 表现为病原菌感染或无菌性炎症诱发，PAMPs、DAMPs 介导下炎性介质的释放、

促炎与抗炎效应失衡。这一过程还可以被先天性免疫系统放大，影响免疫细胞的表型与功能，介导免疫抑制。最终 SI 与免疫功能障碍共同作用加剧感染，引发肝内外器官衰竭，严重危害患者生命健康。虽然 SI 已被证实是 ACLF 发生和发展的重要环节，但其具体的致病机制及不同促炎事件诱发炎症反应的差异性还需要进一步阐明。对于 ACLF 患者病情管理与治疗，肝移植虽是最有效及最终手段，然而肝源不足、匹配困难、治疗费用高昂都严重限制其应用，因此寻找有效的干预措施用来改善炎症反应，延缓器官衰竭及不良结局事件的发生应成为未来研究的关注方向。

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