·综述·

# 肝硬化相关免疫功能障碍的临床意义及研究进展

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【摘要】 肝硬化相关免疫功能障碍(cirrhosis-associated immune dysfunction, CAID)是指肝硬化中存在的广泛的免疫改变。CAID 的特点包含全身炎症和免疫缺陷表现出不同的强度,这取决于肝硬化的阶段和诸如细菌感染等偶发事件的存在。CAID 的治疗应包括调节而非抑制免疫反应,因为消除或刺激炎症反应可能增加感染风险或恶化免疫病理学。本文就肝硬化发生免疫功能障碍的机制及临床意义进行了综述,阐述了改善肝硬化中功能失调的免疫反应的潜在靶点,以期为临床上延缓肝硬化进展及挽救肝衰竭提供参考。

【关键词】 肝硬化;免疫功能障碍;全身炎症;临床;治疗
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**Clinical significance and research progress in cirrhosis-associated immune dysfunction**

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【**Abstract**】 Cirrhosis-associated immune dysfunction (CAID) refers to the extensive immune changes present in cirrhosis. The key components of CAID include systemic inflammation and immunodeficiency, which manifest with different intensity depending on the stage of cirrhosis and the presence of contingencies such as bacterial infections. Treatment of CAID should include strategies to modulate rather than suppress the immune response, as eliminating or stimulating the inflammatory response may increase the risk of infection or worsen immunopathology. This review summarizes the mechanisms and clinical implications of immune dysfunction in cirrhosis, and describes potential targets for improving dysfunctional immune responses in cirrhosis, so as to provide reference for clinically delaying the progression of cirrhosis and salvaging liver failure.

【**Key words**】 Cirrhosis; Immune dysfunction; Systemic inflammation; Clinical; Treatment
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肝硬化的特点是进行性纤维化、门脉高压和肝功能衰竭,它包括两个连续但可能可逆的阶段:代偿性肝硬化和失代偿性肝硬化。肝硬化与免疫功能有着双向的关系:免疫介导的炎症机制在肝硬化的发病机制中发挥作用,肝硬化和门脉高压同样会导致免疫细胞激活失调和免疫损伤[1]。肝硬化患者发生的免疫紊乱的动态谱被称为肝硬化相关免疫功能障碍(cirrhosis-associated immune dysfunction, CAID)[2],它由细菌和细菌产物易位引起的持续免疫细胞刺激引起,在这种持续刺激下,免疫应答系统最终会耗尽,并在失代偿性肝硬化的晚期转变为“免疫缺陷”表型[3]。本文总结了 CAID 的定义、发病机制、临床意义及治疗策略,有助于临床及时准确识别全身炎症强度及免疫紊乱状态,从而减轻这些患者与感染相关的显著死亡率和发病率。

## 一、肝脏在系统性免疫稳态中的作用

肝脏是第一个通过门静脉与源自肠道的细菌和细菌产物接触的器官。肝实质细胞和其他肝脏驻留细胞共同形成一个微调的免疫网络,过滤逃避肠道免疫细胞监测的肠道衍生细菌[4]。

在健康环境中，肠-肝轴允许宿主-微生物群通信，并通过双向调节介导免疫稳态。肠道相关淋巴组织，包括 Peyer's 集合淋巴结、孤立的淋巴滤泡以及固有层和肠系膜淋巴结，形成防御肠道病原体的屏障[5-7]。肝硬化时，肠道微生态失调与肠道屏障受损可能同时发生，容易将病原体及其有毒代谢产物引入系统，导致肝脏和其他肝外器官发生大规模免疫变化[8]。源自肠道微生物的病原体相关分子模式（pathogen-associated molecular patterns, PAMP）通过不同的模式识别受体（pattern recognition receptor, PRR）直接刺激肝细胞和肝脏免疫细胞，损伤肝细胞释放的损伤相关分子模式（damage associated molecular patterns, DAMP）进一步促进了这一过程[7-8]，肝星形细胞和其他免疫细胞有助于这种促炎和促纤维化的转变。

## 二、CAID 的两种病理生理学状态

CAID 是肝硬化环境中免疫系统受损的复杂表现，主要以全身炎症和免疫缺陷为特征[9]。

1.全身炎症

（1）发生机制

PAMP 与不同器官和组织的 PRR 结合，导致促炎细胞因子的大量释放以及各种免疫细胞和炎症小体的激活。此外，内毒素、酒精、胆固醇和活性氧（reactive oxygen species, ROS）等有害元素及其诱导的炎症会导致肝细胞损伤，从而将 DAMP 释放到循环中，进一步加剧全身炎症[10]。与此同时，肝功能受损导致白蛋白不足，白蛋白是一种中和炎症的蛋白质，其合成不足导致机体抗炎及抗氧化应激能力减弱[11]。同样，单核细胞和枯否细胞产生的抗炎细胞因子如 IL-10 的不足会抑制免疫耐受并促进炎症。

PAMP 或 DAMP 与先天免疫系统之间通过特定受体的相互作用驱动炎症介质的全身释放[12]。标准途径为：在识别 PAMP 和 DAMP 后，炎症小体的激活需要促炎细胞因子和炎症小体成分的转录上调、炎症小体的组装和 caspase 1 的裂解[13]。非标准途径为：人类单核细胞对脂多糖（lipopolysaccharide, LPS）的细胞内识别由 caspase 4 和 5（小鼠 caspase 11）介导，并触发一种被称为细胞焦亡的程序性促炎细胞死亡[11,14]。

（2）临床意义及内在机制

促炎细胞因子的直接作用和激活的先天免疫细胞影响肝硬化的临床表现有：（1）对血流动力学及血管张力产生影响：促炎细胞因子刺激内皮细胞一氧化氮和 ROS 过度产生而使外周血管舒张、门静脉高压和心功能不全[15-16]；（2）损伤肾功能：炎症介导的微血管功能障碍可减少肾小球滤过率，促炎细胞因子以及 PAMPs/DAMPs 能够通过肾小球滤过或肾小管近端周围毛细血管到达肾小管，被肾小管上皮细胞通过 TLR4 识别后引发炎症反应，从而导致肾功能不全[17]；（3）改变肝硬化患者的脑信号：促炎细胞因子或募集至大脑组织的活化免疫细胞可活化大脑信号通路，激活局部巨噬细胞产生 TNF-α，造成脑灌注不足和功能障碍，引起肝性脑病及乏力症状[18-19]；（4）全身炎症以及门静脉高压症也推动了失代偿期肝硬化的临床进程，与器官衰竭和生存率密切相关[20-21]。

2.免疫缺陷

（1）发生机制

免疫缺陷定义为免疫系统细胞的异常，损害其效应器功能并导致免疫瘫痪，包括功能缺陷、免疫抑制亚群的扩张或共刺激分子的表达减少[22]。肝硬化患者的免疫缺陷是由肝脏结构和功能的变化以及循环免疫细胞和先天免疫屏障的功能损害两个主要因素造成。

肝脏结构和功能的变化会导致免疫缺陷。细胞外基质沉积、肝窦毛细血管化阻碍了肝内固有 APC 的免疫识别、免疫应答和免疫调节作用。而肝内分流阻止了肠道来源的门静脉和全身细菌被枯否细胞"过滤"和清除[23]。此外，肝细胞丢失会减少免疫蛋白和受体的合成，包括补体成分、可溶性 PRR、白蛋白和肝脏急性期蛋白[24]，可损害肝脏的免疫监测和病原体清除功能。

长期炎症不仅会对实质细胞造成损害，还会对循环免疫细胞造成损害，其功能如吞噬作用、迁移能力、趋化性和 T 细胞活化等均不同程度受到抑制。同样，中性粒细胞在肝硬化进展过程中抗菌活性受损[25]。此外，持续激活使淋巴细胞易出现无应答、细胞凋亡和衰竭。T 细胞产生的 IFN-γ 减少，而抑制信号如 PD-1 和 TIM3 增加[26]。在慢加急性肝衰竭（acute-on-chronic liver failure，ACLF）中，免疫缺陷的特征是单核细胞表面 HLA-DR 的表达下降、TNF 产生受损、IL-10 释放量增加，单核细胞和中性粒细胞的吞噬能力严重受损[27]。

（2）临床结局

肝硬化相关的免疫缺陷涉及先天和适应性免疫细胞，以及调节免疫细胞分化的 PAMP、DAMP、细胞因子、激素和代谢产物，因此失代偿性肝硬化患者极易感染。随着肝硬化的进展，免疫功能恶化，晚期患者尤其是 ACLF 患者，容易受到严重的全身感染[28]。肝硬化住院患者细菌感染的发生率为 25%~47%，最常见的是自发性细菌性腹膜炎（spontaneous bacterial peritonitis, SBP），肺部和皮肤软组织等其他部位感染的发生率逐年上升[29]。感染通常是由先天免疫屏障的破坏和免疫细胞的清除不足引起的，使细菌和细菌产物转移到系统循环；肝硬化患者的持续肝脏炎症已经进入系统循环，引发系统性炎症反应综合征（systemic inflammatory response

syndrome, SIRS)和败血症,使得肝硬化患者在感染的情况下特别容易发生器官衰竭。

## 三、CAID 的治疗方法

CAID 极具挑战性,单纯抑制全身炎症明显会增加感染风险,而刺激炎症反应的方法可能会引起细胞和组织的损伤[30]。因此,CAID 的治疗必须包括调节免疫应答的策略。对于 CAID,目前指南不包括任何直接的免疫调节治疗方法[31-32],但有间接证据表明一些干预措施可能是有益的,这些方法目前正在研究中。

1. 细菌易位的治疗

广谱肠道抗生素利福昔明已被证明可以改善肠道微生物群,减少血清促炎性细胞因子的产生,预防肝性脑病、肝肾综合症和 SBP 的发生,或改善其严重程度[33]。双盲随机对照试验中,诺氟沙星使失代偿期肝硬化患者的感染风险和死亡率显著降低[34-35]。口服肠道吸收剂 Carbalive (Yaq-001)是一种新合成的不可吸收的活性炭,对细菌毒素有高度吸附能力,是 1 种抵御肠道菌群改变和细菌移位的新策略,目前正在Ⅱ期临床试验(NCT03202498)[36]。TAK-242 是一种重要的 LPS 受体 TLR4 抑制剂,在败血症中给予 TAK242 可改善革兰阴性菌感染患者的预后[37],目前正在临床研究中评估其在肝硬化和 ACLF 中的应用。对于肠道屏障恢复,FXR 激动剂奥贝胆酸改善了黏液层的状态,稳定了肠道血管屏障,改善了肠道菌群构成,减少细菌易位[38-39]。

2.针对循环中体液因素的治疗

循环体液因素,如内毒素、前列腺素、ROS、儿茶酚胺和细胞死亡产物的升高,会加重全身炎症和肝硬化[40-41]。白蛋白通过结合这些介质改善炎症、氧化应激,在降低 SBP、肝肾综合征风险和死亡率方面发挥有益作用[42-43]。补充白蛋白可以通过降低 PGE2 的生物利用度来恢复单核细胞功能[44]。白蛋白还可能通过抑制核内体 Toll 样受体(TLR)信号转导发挥免疫调节作用。肝透析设备和血浆交换策略可以去除有害物质,例如新型肝透析设备“DIALIVE”[45]。非选择性 β 受体阻滞剂可减弱儿茶酚胺的作用,改善全身炎症,降低门静脉压,预防食管胃静脉曲张出血,从而降低 ACLF 患者的死亡率[46]。

3.以骨髓为目标的治疗

造血干细胞和间充质干细胞以及各种免疫细胞显著减少,免疫细胞功能不正常,加重全身炎症。粒细胞集落刺激因子(G-CSF)是一种从骨髓中动员 $CD34^+$造血干细胞的强效细胞因子,通过替代功能失调的循环先天免疫细胞(粒细胞、单核细胞和 DC),改善肝硬化的先天免疫反应和肝脏再生。自体干细胞疗法正在开发其改善包括 ACLF 在内的失代偿性肝硬化患者预后的潜力。到目前为止,G-CSF 的使用仍然存在争议,仅限于正在进行的临床试验[47-48]。

4.直接靶向免疫细胞的治疗

代谢组学数据表明,ACLF 患者有严重的线粒体功能障碍,造成氨基酸分解和有毒代谢物生成增加[49]。这种代谢变化与谷氨酰胺有关,谷氨酰胺是维持肠道和免疫健康的一种极其重要的氨基酸,为细胞提供代谢能源,抗炎、抗氧化、降低内毒素水平,调节机体免疫及维护肠黏膜结构和功能[50-51]。然而,这些数据并不一定表明抑制体内谷氨酰胺合成是一种可能的治疗选择,因为这可能会导致高氨血症,从而对肠道功能产生负面影响,而高氨血症本身可能通过 p38 MAPK 途径损害中性粒细胞功能。

细胞信号方面,在失代偿期肝硬化中,先天性和适应性免疫系统的细胞都显示出细胞内信号,导致功能缺陷,从而提供潜在的治疗靶点。激动剂 CL097 激活 TLR7/TLR8 通路可在体外恢复中性粒细胞功能,提供了一种潜在的新治疗方法[52]。ACLF 中单核细胞吞噬和杀菌活性降低与 MERTK 表达的增加有关。UNC56915 (Calbiochem/Millipore, 英国)对 MERTK 的药理学抑制在体外恢复了单核细胞的功能状态,为未来的治疗提供了可能的靶点[53]。此外,在酒精相关 ACLF 患者中,外周血单核细胞表现出缺陷性 T 细胞反应,这与 TIM3 和 PD1 的表达增加有关。对这些蛋白质的体外抑制恢复 T 细胞的反应,表明也许是一种潜在的新疗法[54]。

## 四、结语

肝硬化破坏了肝功能维持体内平衡和肝脏免疫监测的能力,从而导致体内免疫功能障碍。CAID 已被提议从稳定肝硬化的促炎表型转变为失代偿性肝硬化和急慢性肝功能衰竭患者的免疫缺陷表型。CAID 是一个动态过程,随着肝硬化从代偿期发展到失代偿期和 ACLF,全身炎症和免疫缺陷的强度也会增加。CAID 影响肝硬化临床表现包括细菌易感性、血流动力学改变、以及器官炎症损伤,未来阻止这一进展的干预措施应在不同水平上进行试验,包括肠道微生物组、肠道屏障以及肠道、肝脏和全身免疫细胞等。

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