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免疫衰老与肝移植术后感染：从生物学机制到临床预后的深度评估

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摘　要

肝移植术后感染是影响受者长期生存的主要障碍。近年研究发现，免疫衰老——以衰老相关分泌表型(SASP)驱动的炎性衰老、髓系偏移及肠道菌群失调为特征——是决定术后感染易感性与移植物预后的关键因素。在肝移植受者中，该过程受供肝年龄、缺血再灌注损伤及长期免疫抑制共同加剧，表现为CD4+T细胞与NK细胞重建延迟、T细胞受体多样性降低及代谢重塑。临床研究证实，免疫衰老状态与多重耐药菌感染、潜伏病毒再激活及严重脓毒症风险显著相关，血清IL-6、TNF-α等炎症标志物可作为预测感染严重程度和生存率的独立指标。针对性地清除衰老细胞、调控肠道微生态、阻断特定炎症通路及优化免疫策略，有望重建受者免疫稳态。未来将免疫衰老标志物整合至临床风险评估体系，对实现肝移植术后个体化感染防控具有重要意义。

关键词

肝移植，免疫衰老，术后感染，炎性衰老，微生态失调，衰老细胞清除

Immune Aging and Post-Liver Transplant Infection: A Comprehensive Assessment from Biological Mechanisms to Clinical Outcomes

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Abstract

Post-liver transplantation infection is the main obstacle affecting the long-term survival of recipients. Recent studies have found that immunosenescence-characterized by inflammatory senescence driven by senescence-associated secretory phenotype (SASP), myeloid shift, and intestinal flora imbalance is a key factor determining the susceptibility to postoperative infection and the prognosis of the graft. In liver transplant recipients, this process is exacerbated by donor liver age, ischemia-reperfusion injury, and long-term immunosuppression, manifested as delayed reconstitution of CD4+T cells and NK cells, reduced T cell receptor diversity, and metabolic remodeling. Clinical studies have confirmed that the immunosenescent state is significantly associated with multi-drug resistant bacterial infections, reactivation of latent viruses, and the risk of severe sepsis. Inflammatory markers such as serum IL-6 and TNF-α can be used as independent indicators for predicting the severity of infection and survival rate. Targeted elimination of senescent cells, regulation of the intestinal microbiome, blocking specific inflammatory pathways, and optimizing immunological strategies are expected to restore the immune homeostasis of recipients. Integrating immunosenescent markers into the clinical risk assessment system is of great significance for achieving individualized infection prevention and control after liver transplantation.

Keywords

Liver Transplantation, Immunosenescence, Postoperative Infection, Inflammaging, Microecological Dysbiosis, Senolytics

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1. 引言

肝移植(Liver Transplantation, LT)作为治疗终末期肝病、暴发性肝衰竭及部分肝脏恶性肿瘤的基石方案，其临床成功已通过显著提升的生存率得到证实：受者 5 年生存率跨越了 70%的门槛[1] [2]。然而，肝移植术后仍然面临着诸多挑战。细菌感染，尤其是由革兰氏阴性菌(如肠杆菌属、肺炎克雷伯菌)和多重耐药(MDR)细菌引发的感染，依然是肝移植受者发病率和死亡率的首要诱因[2] [3]。肝移植受者的免疫系统在围手术期经历着剧烈的“重塑”。手术创伤本身以及不可避免的缺血再灌注损伤(IRI)触发了强烈的全身炎症反应综合征[4]。为了抑制同种异体排斥反应，受者必须接受长期的免疫抑制治疗。这种药物诱导的微环境不仅增加了感染风险，还深度干预了免疫细胞的动态平衡[5] [6]。相关研究指出，不同免疫抑制方案对中性粒细胞、NK 细胞以及 CD8+T 细胞的重建过程有差异性影响，这种免疫重建延迟现象与术后早期的高感染风险期存在直接联系[7]，随着供体短缺问题加剧，高龄供体的应用比例逐年上升，阿根廷学者的单中心研究证实，供肝的生物学年龄与受者的总体生存率以及移植物存活率呈负相关。老年供肝中积累的脂褐素沉积、上调的促炎基因表达以及十分突出的细胞衰老特征，可改变受体的免疫微环境[8]，最新研究说明，老年移植物可借助释放线粒体 DNA 等衰老相关分泌表型因子，在年轻受体中诱发异位衰老效应，损害其认知及躯体功能[9]，虽然传统观点将术后感染主要归因于免疫抑制剂的副作用，但“免疫衰老”概念的引入为长期预后评估提供了新的理论框架[10]。这一病理生理过程表现为免疫系统随年龄增长出现的功能性衰退，其特征包括病原体应答能力降低以及持续性低度炎症状态[11] [12]，在肝移植

领域，免疫衰老作为独立于血药浓度的生物学变量，正逐渐成为评估移植效果及感染易感性的关键指标[10] [13]。

2. 免疫衰老的核心生物学机制

免疫衰老并非免疫力的整体归零，而是一场跨越骨髓、肠道及全身循环的病理生理重构。

2.1. 炎性衰老

炎性衰老(Inflammaging)是免疫衰老的标志性特征。其表现为机体长期处于一种促炎因子失衡的状态[14] [15]。针对 COVID-19 的研究发现，高水平的血清白细胞介素-6 (IL-6)、IL-8 以及肿瘤坏死因子-α (TNF-α)不仅是病毒感染严重程度的预测因子，更是评估机体基础免疫年龄的敏感指标[16]。这种持续的炎症背景会加速 T 细胞的耗竭，并使固有免疫细胞在面对突发感染时反应迟钝[17] [18]。

2.2. 骨髓生态位与造血系统的“髓系偏移”

免疫系统的退化源于造血根源。随着老化，造血干细胞(HSC)表现出明显的分化潜能偏斜，其分化方向更倾向于产生髓系细胞而非淋巴系细胞[19] [20]。这种偏移导致中性粒细胞和单核细胞虽然数量可能增加，但其吞噬与杀伤功能往往存在缺陷，而抗感染的核心力量——T 细胞和 B 细胞的产出则显著萎缩[21]-[23]。

2.3. 肠道微生态：免疫老化的“驱动泵”

肠道微生物群落与宿主免疫系统存在深度耦合。人类白细胞抗原(HLA)单倍型通过调控 T 细胞与 NK 细胞的特异性，塑造了肠道菌群的结构[24]。研究显示，微生物群落的多样性(Alpha 多样性)与宿主免疫基因的表达密切相关[25]-[27]。当发生随年龄增长的菌群失调时，肠道屏障通透性增加，导致微生物组分进入循环系统，通过 TNF 路径诱导巨噬细胞功能障碍并加剧全身性炎症。这种由菌群驱动的炎症反应，正是诱导系统性免疫衰老的关键因素[28] [29]。

2.4. 免疫抑制网络的恶性扩张

为了对抗慢性炎症带来的组织损伤，机体演化出了一个庞大的补偿性抑制网络。在炎性因子的刺激下，骨髓源性抑制细胞(MDSC)、调节性 T 细胞(Treg)和 M2 型巨噬细胞在体内异常聚集[12] [30]。这些细胞通过释放转化生长因子-β (TGF-β)、IL-10、精氨酸酶-1 (ARG1)等因子，不仅抑制了 CD4+/CD8+T 细胞的增殖，还导致了自然杀伤(NK)细胞和树突状细胞的功能麻痹[31]-[34]。

3. 免疫衰老在肝移植受者中的内在表现

3.1. 淋巴细胞亚群的失衡与耗竭

在肝移植及相关骨髓移植后的免疫重建过程中，CD4+T 细胞和 NK 细胞的快速恢复被证实具有关键的保护作用，特别是对抗巨细胞病毒(CMV)的重激活[35]。然而，在免疫衰老背景下，这些关键细胞的重建往往严重滞后。此外，随着受体年龄或供肝年龄的增加，受者体内的淋巴细胞表现出明显的衰老标志：原始 T 细胞比例锐减，而终末分化的效应记忆 T 细胞(TEMRA)比例升高[36] [37]。这类细胞表面衰老标志物(如 sCD163，sCD28，sCD80，sCTLA-4)水平的升高，预示着免疫防御能力的枯竭[38]。

3.2. 代谢环境对免疫表型的重塑

肝移植不仅是器官的置换，更是全身代谢环境的剧烈变迁。年轻的供体肝脏在进入老年受体环境后，受其血清代谢环境的影响，在短短几周内其组织代谢谱便会向老年表型靠拢，涉及甘油磷脂、花生四烯

酸等关键代谢通路的改变[39] [40]。这种代谢与免疫的互作进一步固化了受体的衰老表型。

3.3. 疫苗应答的异质性与免疫保护力缺损

免疫衰老最直观的临床表现是受者对疫苗接种的反应性下降[41]。在针对 SARS-CoV-2 疫苗(BNT162b2)的研究中发现，80 岁以上个体的抗体中和滴度显著低于年轻组，且在接种第一剂后往往完全缺乏对变异株(如 Alpha，Beta，Gamma)的中和能力[42]。这种抗体产生的迟滞以及 IFN-γ 分泌能力的下降，反映了受者在免疫监控层面的整体衰退。

3.4. 常用免疫抑制剂对细胞衰老及 SASP 的调节作用

在肝移植临床实践中，免疫抑制剂不仅是预防排斥反应的基石，也是重塑受者免疫微环境的核心变量。传统观点主要关注其对免疫细胞增殖的抑制作用，但近年来的深度评估发现，不同机制的药物对细胞衰老进程及衰老相关分泌表型(SASP)具有截然不同的调节效应。钙调磷酸酶抑制剂(CNIs)，如他克莫司，通过长期抑制 T 细胞活化，可能在宏观上加速免疫系统的衰老效应，诱导淋巴细胞出现过度耗竭表型[43]。此外，长期应用 CNIs 与全身性低度炎症(炎性衰老)的维持密切相关，可能通过增加细胞内的氧化应激水平，间接促进 SASP 因子的释放，从而固化受体的衰老表型[44]。相比之下，哺乳动物雷帕霉素靶蛋白抑制剂(mTORi)，如雷帕霉素，则展现出显著的延缓衰老效应。mTOR 是调控 SASP 合成的关键节点，雷帕霉素能够通过阻断该通路，有效抑制 IL-6、TNF-α 等促炎因子的翻译，减轻由 SASP 驱动的系统性炎症[45] [46]。而对于麦考酚酯(MMF)，其通过抑制 DNA 合成来干预细胞周期，这种强制性的停滞在特定微环境下可能诱导细胞进入非增殖的类衰老状态，并通过代谢重塑进一步影响受者的免疫表型[47]。

4. 免疫衰老与特定感染的关联

4.1. 细菌性感染与多重耐药性

肝移植术后，受者常面临肠源性细菌易位的威胁。由于免疫衰老导致的肠道通透性增加及巨噬细胞功能障碍，受者对革兰氏阴性菌(如假单胞菌、克雷伯菌)的清除效率大幅降低[48] [49]。此外，由于这种免疫脆弱背景，受者更容易演变为多重耐药菌(MDR)感染，使得临床管理愈发困难[50] [51]。

4.2. 病毒重激活：以 CMV 为例

在免疫功能完善的个体中，CMV 处于休眠状态。但在免疫衰老的肝移植受者中，由于 CD4+T 细胞和 NK 细胞无法形成有效的免疫包围圈，病毒重激活风险显著增加[52]。研究揭示，术后早期淋巴细胞重建的深度和广度是预防病毒性并发症的关键指标，而免疫衰老恰恰是这一重建过程的最大障碍[53]。

4.3. 脓毒症与多器官功能损害

脓毒症在免疫衰老背景下具有更长的病理轨迹。衰老相关的免疫细胞凋亡增加、胸腺变性及免疫抑制细胞的增殖，与脓毒症诱导的免疫麻痹高度契合。这解释了为何高龄或衰老指标异常的受者在发生感染后，往往伴随更高的 SOFA 评分和更差的器官损伤预后[54] [55]。

5. 靶向免疫衰老的潜在治疗策略

5.1. 衰老细胞清除(Senolytics)的应用

清除衰老细胞(p16Ink4a 阳性细胞)已被证实在酒精性肝病等模型中能够有效减轻氧化应激和脂质积聚，并促进 M1/M2 巨噬细胞向保护型极化[56]。更有前瞻性的研究显示，在移植前对老年供体器官进行 Senolytics 处理，可显著减少由于 mt-DNA 释放引发的系统性衰老，从而改善年轻受体的预后[9]。衰老细

胞清除(Senolytics)的应用虽然在减轻组织氧化应激和促进巨噬细胞极化方面展现出前景，但其安全性仍需警惕。一方面，大规模清除衰老细胞可能移除部分具有免疫调节功能的细胞亚群，破坏移植物内部的免疫稳态；另一方面，衰老细胞凋亡过程中释放的损伤相关分子模式(DAMPs)可能在短期内激活受者的免疫系统，诱发急性排斥反应[57] [58]。

5.2. 系统免疫学驱动的精准评估

利用系统免疫学(Systems Immunology)工具对受者的细胞构成、血浆蛋白和功能应答进行非随机化的变异分析，有助于识别人群中的免疫易感特征[59]。通过监测血清中 sCD163 等可溶性标志物，临床医生可以超越传统的血药浓度监测，实现对受者真实免疫风险的分层管理[60]。

5.3. 疫苗策略的优化与强化

鉴于老年及衰老受体对标准接种方案的低反应性，采用更高剂量的抗原、新型佐剂或多剂次(三剂及以上)的加强免疫方案是必要的防护手段[61]。同时，结合术后 NK 细胞与 CD4+T 细胞的快速重建动力学，适时调整免疫支持强度，可有效降低病毒重激活的发生率[41]。

5.4. 肠道微生态修复与类器官模型

通过饮食干预、益生菌补充或针对性的微生态疗法，降低肠道通透性并减轻由 TNF 介导的炎症反应，为缓解系统性免疫衰老提供了新思路[62] [63]。此外，利用肝脏或肠道类器官技术进行体外模型构建，将有助于我们在更接近人体生理的环境下筛选能逆转免疫衰老的小分子药物[64]。

6. 总结与展望

肝移植受者的术后感染风险已不能仅归因于传统免疫抑制，免疫衰老作为核心生物学变量，通过“炎性衰老”、髓系偏移、肠道微生态失调等机制，系统性削弱宿主防御功能，显著增加对多重耐药菌、潜伏病毒及脓毒症的易感性。未来研究需建立整合供肝年龄、受体免疫谱及微生物组的多维度风险评估体系，并推动靶向衰老细胞、重塑肠道生态及优化疫苗策略的个体化干预。通过跨学科融合系统免疫学与移植医学，有望实现对免疫衰老的精准调控，从而提升肝移植受者的长期生存质量与感染防控成效。

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