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脓毒症免疫抑制与肠道菌群失调

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摘要 晚期脓毒症患者长期的免疫抑制是其高死亡率的主要原因. 持续的免疫抑制不仅不利于对原始感染源的控制, 还增加多重耐药菌和条件致病菌二次感染的风险. 逆转脓毒症患者的免疫抑制状态对于改善其生存率具重要意义. 肠道菌群失调可通过多种机制增加个体对脓毒症的易感性. 本综述旨在探讨脓毒症免疫抑制的机制, 分析肠道菌群在其中的角色, 特别是对脓毒症免疫抑制的形成和进展的可能影响.

关键词 脓毒症, 肠道菌群失调, 免疫抑制

脓毒症是人体对感染反应失调导致的器官功能障碍, 是临床危重病患者的重要死亡原因之一, 呈现发病率高、死亡率高且治疗费用高的特点. 近年来虽发病率略有下降, 但全球脓毒症死亡人数仍占总死亡人数的五分之一[1]. 脓毒症患者的治疗成本高昂, 病情好转出院的患者, 也可能面临长期的身体机能减退、心理健康障碍及认知功能障碍等, 对患者后续的生活造成不良影响[2]. 当前, 脓毒症的治疗主要依赖支持性疗法, 缺乏针对性的干预手段[3]. 深入研究脓毒症的发病机制, 探索新的治疗靶点, 对其防治具有重要的理论和临床意义.

脓毒症患者炎症反应和抗炎反应失衡并持续存在, 造成持续或反复感染, 以及器官功能持久损害[4]. 脓毒症后期, 抗炎反应占据主导地位, 其所致的免疫抑制是其病死率高的主要原因, 20%~40%的患者死于免疫抑制[5]. 脓毒症患者的免疫抑制状态主要表现为效应细胞凋亡, T细胞耗竭, 单核细胞的人类白细胞抗原-DR(human leukocyte antigen-DR, HLA-DR)表达减少, 抗原提呈能力减弱, 细菌清除能力下降, 髓系抑制细胞(myeloid-derived suppressor cells, MDSCs)数量增加等[6]. 持续的免疫抑制不仅不利于感染源的控制, 还易诱发多重耐药菌或条件致病菌的继发性感染而无法控制, 严重影响患者预后, 调节免疫抑制状态对改善脓毒症患者的治疗效果至关重要.

越来越多的研究关注到宿主肠道菌群失调在脓毒症发生发展中的作用, 脓毒症患者的肠道菌群呈现多样性减少, 厚壁菌门和拟杆菌门丰度降低, 共生菌数量减少, 条件致病菌过度增长等特点[7~9]. 肠道菌群的改变可通过多种机制增加脓毒症的易感性, 包括致病性肠道细菌的扩增、破坏机体免疫平衡, 以及减少有益微生物产物等等[10]. 本文将综述脓毒症免疫抑制的

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机制、肠道菌群在脓毒症中的作用，特别是对脓毒症免疫抑制的发生发展的可能影响.

1　脓毒症免疫抑制的机制

脓毒症患者对感染反应失衡，初期产生过度炎症反应，随后因炎症介质消耗、免疫细胞功能受损以及调节性免疫细胞活性增强, 常出现免疫抑制现象[6]. 免疫调节剂的使用能有效改善脓毒症患者的预后，降低医疗成本[11]. 脓毒症的免疫抑制主要表现为免疫细胞功能失调，抑制型受体过表达，促炎细胞因子表达减少和抗炎细胞因子释放增加等等[12](图1).

1.1　中性粒细胞功能降低

中性粒细胞作为重要的天然免疫效应细胞，在脓毒症早期展现出活跃的迁移、吞噬和杀伤细菌等行为, 而脓毒症后期, 中性粒细胞耗竭, 病原体清除能力下降，助推脓毒症免疫抑制的发生发展[13]. 全血单细胞测序显示，脓毒症患者中免疫抑制性中性粒细胞和未成熟的中性粒细胞比例显著高于健康个体[14]. 脓毒症免疫抑制患者的多形核中性粒细胞(polymorphonuclear neutrophils, PMNs)生成障碍, PMNs发生显著的代谢重编程和表观遗传学变化[15]，其表面标志物表达也呈现出明显的变化[16]. 正常情况下, PMNs主要依赖糖酵解快速产能，以应对病原体感染时的能量需求[17]，但脓毒症时脂多糖(lipopolysaccharide，LPS)耐受的PMNs的糖酵解被抑制[13]，PMNs能量供应不足，迁移、吞噬和杀菌能力下降. 此外, LPS刺激后中性粒细胞表达的程序性死亡配体1(programmed cell death ligand 1, PD-L1)显著升高[18]. PD-L1与$CD4^+$ T淋巴细胞上的程序性死亡受体1(programmed cell death protein 1, PD-1)结合, 抑制T细胞的活化, 诱导T细胞凋亡和转分化, 进一步加剧免疫抑制状态[18].

1.2　单核细胞和巨噬细胞呈现抗炎表型

单核细胞作为巨噬细胞的前体，自骨髓释放入血，到组织中分化成为不同种类的巨噬细胞，在免疫炎症中发挥重要作用[19]. 在脓毒症免疫抑制患者中，单核细胞和巨噬细胞数目显著降低，呈现抗炎表型，抗原呈递能力也显著下降[20,21]. 单核细胞和巨噬细胞所表达的HLA-DR可以作为评价其功能的标志物，脓

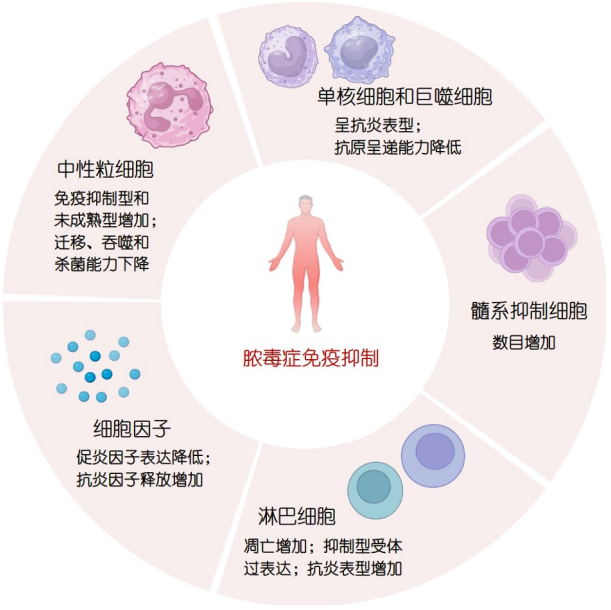

图 1　脓毒症免疫抑制. 脓毒症免疫抑制主要表现为，中性粒细胞功能降低，单核细胞和巨噬细胞呈现抗炎表型，髓系抑制细胞增加, 淋巴细胞凋亡, 以及细胞因子水平的改变

Figure 1　Sepsis immunosuppression. Sepsis immunosuppression is characterized by decreased neutrophil function, an anti-inflammatory phenotype of monocytes and macrophages, an increase in bone marrow-derived suppressor cells, lymphocyte apoptosis, and altered cytokine levels

毒症免疫抑制患者血清中HLA-DR水平下降[22,23]，进而影响抗原提呈和T细胞激活，加剧免疫抑制状态. HLA-DR低水平的脓毒症患者发生院内感染和死亡的风险增加[24,25]. 脓毒症免疫抑制患者的单核细胞和巨噬细胞中还会出现T细胞免疫球蛋白和黏蛋白结构域 4(T-cell immunoglobulin and mucin domain-4, TIM-4)和Nod样受体蛋白3(Nod-like receptor protein 3, NALP3)炎症小体表达的下调[23]. 缺氧诱导因子-1α (hypoxia-inducible factor-1 alpha, HIF1α)信号通路在单核细胞表型从促炎状态转变为免疫抑制状态中发挥重要作用[26,27]. 脓毒症免疫抑制过程中促炎的M1型与抗炎的M2型巨噬细胞失衡[28]. 脓毒症后晚期与M1型巨噬细胞有关的促炎因子，如肿瘤坏死因子(tumor necrosis factor alpha, TNF-α)、白细胞介素-1β (interleukin-1β, IL-1β)、IL-6和IL-12水平显著降低，与M2型巨噬细胞相关的抗炎因子IL-10显著升高，这些都与脓毒症后期易感性增加和免疫抑制密切相关[29]. 近期研究通过单细胞测序发现，单核细胞中存在一群具有免疫抑制效应的新亚群. 该亚群以HLA-

DR低表达以及S100A家族基因高表达为显著特点, 能显著抑制$CD4^+$ T细胞的增殖, 促进$CD4^+$ T细胞向调节性T细胞(regulatory T-cell, Treg)细胞分化, 增加IL-4和IL-10的表达, 抑制IL-2和干扰素γ(Interferon-gamma, IFN-γ)的释放, 与脓毒症免疫抑制状态高度相关[30].

1.3 MDSCs增加

脓毒症时在IL-1β和TNF-α等细胞因子的作用下, 髓系来源的前体细胞成熟受阻, 停留在不同的分化阶段, 成为具有免疫抑制功能的MDSCs[24]. MDSCs显著抑制T细胞增殖及相关促炎因子分泌, 使IL-10与TNF-α的比值增加[31~33]. CCAAT/enhancer结合蛋白β(CCAAT/enhancer binding protein β, C/EBPβ)可能介导MDSCs的生成[34], 降低C/EBPβ的表达可减轻MDSCs对脓毒症造成的免疫抑制[35]. 长链非编码RNA肺腺癌转移相关转录本1(metastasis associated lung adenocarcinoma transcript 1, Malat1)则可通过加速磷酸化的信号转导和转录激活因子3(signal transducer and activator of transcription 3, STAT3)的降解, 限制MDSCs的分化, 提高脓毒症的生存率[36].

1.4 淋巴细胞耗竭

脓毒症免疫抑制患者的淋巴细胞数目显著降低, 凋亡增多, 增殖减少[37]. 淋巴细胞的凋亡与脓毒症的严重程度以及脓毒症患者的预后密切相关[38,39]. 脓毒症小鼠模型中早期就可观察到$CD8^+$T细胞的凋亡, 小鼠体内促炎因子IFN-γ水平显著降低, 脓毒症死亡率升高[40]. 当T淋巴细胞接收到凋亡信号时, Caspase级联反应激活, 激活的Caspase-9剪切体参与凋亡的启动阶段, 激活的Caspase-3剪切体能切割多种底物, 导致细胞结构破坏和功能丧失, 推动细胞凋亡. 脓毒症小鼠$CD4^+$和$CD8^+$ T细胞的caspase-3剪切体和caspase-9剪切体表达显著升高[41]. $CD4^+$ T细胞在脓毒症的后期分化转变, 抗炎的Th2细胞和Treg细胞的反应明显高于促炎的Th1细胞和Th17细胞[42], 抗炎细胞因子分泌增加, 加剧免疫抑制. Treg通过多种机制抑制T细胞活化, 同时影响中性粒细胞和单核细胞凋亡[43,44]. 脓毒症免疫抑制患者中B细胞成熟受损导致B细胞数量减少, 抑制体液免疫, 增加继发感染风险. 记忆B细胞和抗体分泌细胞的数量以及血清免疫球蛋白M(immunoglobulin M, IgM)水平与脓毒症的预后密切相关, 提高B细胞和IgM的水平可有效改善患者预后[45,46].

抑制型受体的过表达是导致T细胞耗竭的重要因素之一. 这些受体, 包括PD-1、细胞毒T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen-4, CTLA-4)、B淋巴细胞和T淋巴细胞衰减剂(B and T lymphocyte attenuator, BTLA)、TIM-3等[47], 可与抗原呈递细胞(Antigen-presenting cells, APC)表面的配体结合, 抑制T细胞的活化并诱导其凋亡[41]. 其中研究最多的是PD-1, 其过表达显著抑制免疫细胞的活化、增殖和免疫功能, 导致脓毒症患者的免疫功能降低[48]. $CD4^+$ T细胞和Treg细胞表面PD-1和CTLA-4的高表达与脓毒症严重程度及预后不良密切相关[49]. 阻断PD-1和CTLA-4可改善脓毒症的生存率[50]. $CD4^+$ T细胞上TIM-3的过表达可促进脓毒症早期自然杀伤T细胞(natural killer T cell, NKT)的凋亡和单核细胞稳态的失衡, 增加脓毒症患者病死率[51~53]. BTLA是在T细胞和B细胞表面表达的共抑制性受体[50], 可抑制淋巴细胞活化促进凋亡[54]. 这些抑制型受体的过表达抑制脓毒症的免疫系统, 加剧免疫抑制状态.

1.5 细胞因子表达改变

脓毒症是一种严重的全身性炎症反应, 伴随着大量的炎症介质的释放和参与. 这些细胞因子在脓毒症的发生、发展和预后方面发挥着重要作用. 脓毒症免疫抑制患者中TNF-α, IFN-γ, IL-1β, IL-2和IL-6等促炎因子的水平显著降低, 导致免疫抑制状态[55,56]. 在脓毒症小鼠模型中, 早期促炎因子TNF-α, IL-1β和IL-6的mRNA水平显著上升, 但随后呈下降趋势, 特别是在免疫抑制阶段表达明显降低[57]. 提高脓毒症小鼠促炎细胞因子水平, 如TNF-α, IL-6, 能有效降低脓毒症免疫抑制患者的死亡率[41,58]. 脓毒症免疫抑制还表现有抗炎细胞因子的水平增加[59]. 在脓毒症后期, MDSCs活化并分泌大量抗炎细胞因子, 如IL-4, IL-10, IL-33和转化生长因子β(transforming growth factor-β, TGF-β)[60,61]. 这些抗炎细胞因子的显著升高与脓毒症免疫抑制紧切相关[62]. IL-10的水平在死亡的脓毒症患者中普遍高于预后良好的患者[63]. IL-10可抑制促炎细胞因子TNF-α和IL-1β的表达[64] , IFN-γ/IL-10可作为脓毒症患者免疫状态的潜在标志物[65].

2　肠道菌群失调对脓毒症免疫抑制的潜在影响

早在30多年前Carrico[66]及其同事就提出假说，在危重疾病期间，肠道上皮通透性会变高，肠道菌群进入血液循环，进而可能导致全身炎症和器官衰竭. 近年来越来越多的研究表明，肠道微菌群失调与脓毒症的发生发展密切相关. 肠道菌群的破坏严重程度与脓毒症的易感性和不良结局风险增加呈正相关[67,68]. 正常情况下，共生菌可刺激抗菌物质分泌，促进细胞间黏附分子的表达，维持肠道的屏障功能，还可调节炎症信号转导，诱导Treg细胞，抑制肠道中炎症的发生[69]. 在脓毒症期间, 肠道菌群的组成被严重扰乱, 共生菌减少, 潜在病原微生物的过度生长, 进而影响免疫反应并增加肠道屏障通透性，肠道细菌和内毒素移位进入血液循环，引发全身性的炎症反应[70~72](图2). 抗生素对特定微生物的抑制和杀灭可导致肠道菌群的结构发生显著改变, 使用抗生素后, 耐碳青霉烯类肺炎克雷伯菌(carbapenem-resistant *Klebsiella pneumoniae*, CRKP)和耐万古霉素屎肠球菌(vancomycin-resistant *Enterococcus faecium*, VRE)等耐药细菌的富集，是引起脓毒症患者继发感染的主要原因[73,74]. 基于微生物组的疗法，如益生菌、粪便微生物群移植和共同饲养等，有助于恢复肠道菌群结构，降低炎症和脓毒症风险，改善脓毒症患者的预后[75,76]. 脓毒症期间肠道菌群代谢物的产生和分布也会发生变化，进而影响宿主的肠道屏障功能和免疫反应, 助推脓毒症的进程[77~81].

肠道被认为是人类最大的免疫器官，肠道菌群和免疫系统的免疫细胞相互作用共同维持肠道的免疫功能和稳态[82]. 肠道菌群不仅能够抵抗病原体对肠道的伤害，保护胃肠道，而且对于肠道黏膜的建立、肠道中黏液的分泌以及免疫系统的发育过程都有重要意义[83,84]. 微生物群从出生开始就逐步在胃肠道中定植, 参与包括肠道屏障免疫在内的宿主生理过程[83]，影响宿主免疫系统的发展和免疫应答. 肠道共生菌通过与

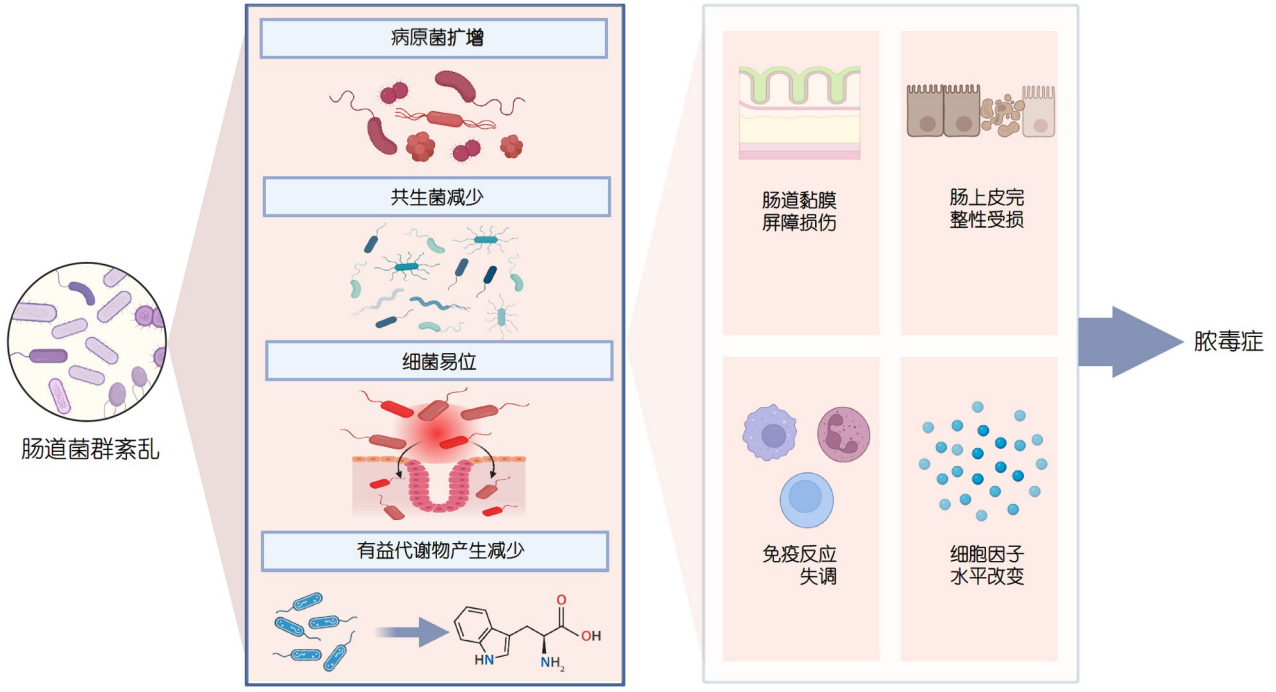

图 2　肠道菌群失调参与脓毒症的机制. 脓毒症患者肠道菌群的组成被严重扰乱, 潜在病原微生物的过度生长, 有益共生菌减少, 肠道菌群代谢产物也发生显著的变化, 进而影响免疫反应和肠道屏障功能, 肠道细菌和内毒素移位进入血液循环, 影响全身性的炎症反应

Figure 2　Mechanism of gut microbiota dysbiosis involved in sepsis. The composition of the gut microbiota in patients with sepsis is severely disrupted, with overgrowth of potential pathogenic microorganisms, reduction of beneficial symbiotic bacteria, and significant changes of microbiota metabolites, which in turn affect the immune response and intestinal barrier, and the intestinal bacteria and endotoxins migrate into the blood circulation, affecting the systemic inflammatory response

sIgA结合，将细菌成分呈递给树突状细胞而影响宿主的先天性免疫. 肠道菌群也可以介导中性粒细胞的迁移影响某些淋巴细胞的分化发育，进而影响不同细胞因子的分泌和机体的免疫状态[84]. 老年小鼠微生物组稳定性下降，脓毒症幸存老年小鼠可出现持续的炎症、免疫抑制和分解代谢状态, 并导致更差的预后[85]. 肠道菌群中的嗜酸乳杆菌可上调肠道内IL-22和IL-33水平, 促进病原体的清除和肠道上皮细胞的恢复, 维持肠道的屏障功能[86]; 除肠道菌群本身，肠道菌群的代谢物异常也会对脓毒症的免疫系统造成影响.

2.1 肠道菌群失调与细胞因子

肠道菌群失调可使具有抗炎能力的细菌和具有促炎潜能的细菌之间的平衡发生改变，进而影响免疫细胞调控机体促炎与抗炎细胞因子的释放[87]. TNF-α, IL-1β和IL-6等促炎因子对肠道菌群和肠道保护屏障都具有重要作用[88~90]. 肠道菌群的LPS通过调节细胞因子对肠道免疫也具有重要作用. 肠道菌群的LPS刺激肠上皮细胞(intestinal epithelial cells, IECs)上的Toll样受体5(Toll-like receptor 5, TLR5), 启动IL-23/22轴, 在肠道的宿主防御中起到重要作用[91]. 抗生素治疗流感病毒感染后的呼吸道黏膜中共生菌促进的IL-1β和IL-18前体产生受损，进而影响机体免疫细胞和IFN-γ的产生，TLR激动剂治疗则可缓解由抗生素治疗的免疫损伤[92]. 这提示肠道菌群可通过影响特定细胞因子的水平在脓毒症免疫抑制中发挥重要作用.

2.2 肠道菌群失调与免疫相关细胞

正常的肠道菌群对于维持机体内的免疫细胞比例十分重要，在肠道黏膜免疫稳态中发挥重要的调节功能[93]. 正常肠道菌群的定植与机体内Th17/Treg的平衡密切相关, 肠道菌群通过影响Th17和Treg的水平, 调节肠道免疫状态[94]. 一旦肠道菌群平衡遭到破坏，将影响肠道中T细胞的生长和分化，加重肠黏膜免疫功能紊乱，促进肠道细菌移位增加[95]. 当肠道组织发生炎症性损伤时, Treg可抑制Th17, 发挥抗炎作用, 抑制肠道过度的免疫反应[96]. 梭状芽孢杆菌作为肠道共生微生物群中最主要的微生物, 可以诱导结肠Treg细胞, 抑制炎症反应[97]. 通过粪菌移植(fecal microbiota transplantation, FMT)重塑肠道菌群可以显著改善Th17/Treg失衡，恢复Th17/Treg的平衡和免疫稳态[98]. 以上研究提示, 肠道菌群可通过影响Th17/Treg等免疫细胞的比例, 影响机体免疫状态, 在脓毒症免疫抑制中发挥作用.

2.3 肠道菌群的代谢物失调与脓毒症免疫状态

抗生素处理后，小鼠肠道菌群物种种类的数量显著减少，肠道共生菌发酵膳食纤维产生的短链脂肪酸(short chain fatty acids, SCFAs)水平也大幅下降[99]. SCFAs可增强巨噬细胞的吞噬作用，调节免疫细胞的功能，调节炎症反应. 微生物来源的SCFA丁酸盐可促进细胞代谢, 对$CD8^+$ T细胞的长期存活和免疫细胞的功能具有积极作用[79]. SCFAs还可通过激活G蛋白受体41(G protein-coupled receptor 41, GPR41)和抑制组蛋白去乙酰化酶(histone deacetylase, HDAC), 促进$CD4^+$ T细胞和固有淋巴细胞(innate lymphoid cell, ILC)产生IL-22, 进而诱导上皮细胞产生抗菌肽、黏蛋白等以维护肠道屏障功能[80,81]. 肠道中SCFAs还可通过下调介导细胞焦亡的核苷酸结合寡聚结构域、富亮氨酸重复序列和含吡啶结构域3(nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3, NLRP3)和gasdermin D-N (GSDMD-N)的表达，减少炎症因子IL-1β和IL-18的释放，抑制细胞焦亡过程，对脓毒症患者具有保护作用[100,101].

脓毒症患者体内多种芳香族氨基酸代谢物减少, 以色氨酸等的代谢变化最为突出[77]. 色氨酸代谢物主要通过对Treg细胞的调控维持机体的免疫耐受. 其中吲哚，2-羟吲哚，吲哚-3-乙酸和犬尿喹啉酸是主要的芳烃受体(aryl hydrocarbon receptor, AhR)激活剂[102]. 色氨酸代谢物可通过AhR相关信号通路抑制巨噬细胞中抗炎因子的分泌[103]. 这些色氨酸代谢物也会对树突状细胞(dendritic cells, DCs)、B细胞、ILC等表达AhR的免疫细胞产生作用, 诱导免疫细胞产生IL-10、IL-22等细胞因子[104~106]. 白色念阿珠菌的代谢产物苯丙酮酸(phenylpyruvic acid, PPA)也可增强巨噬细胞的杀菌活性, 其在脓毒症患者肠道内的含量减少, 巨噬细胞杀菌能力降低[94].

综上所述，肠道菌群及其代谢物能够影响细胞因子和免疫细胞的功能，进而对免疫系统产生影响. 未来研究可进一步明确与脓毒症免疫抑制相关的肠道菌群及其代谢物，通过给予特定的肠道菌群或其代谢物，

在脓毒症动物模型中验证它们对脓毒症免疫抑制的影响，并进一步分析特定肠道菌群或其代谢物对免疫细胞功能和细胞因子表达的影响，揭示其影响脓毒症免疫抑制的机制, 为脓毒症的治疗提供新的思路和方法.

3　脓毒症免疫抑制的治疗

随着对脓毒症的理解逐渐加深，发现脓毒症患者的死亡主要发生在后期的免疫抑制阶段，研究人员开始将脓毒症的治疗方向从控制炎症发展和抑制免疫系统转向刺激患者免疫系统[33]. 目前研究者陆续提出多种用于脓毒症免疫抑制的治疗方法. 巨噬细胞表达的Spinster同源物2(Spinster homolog 2, Spns2)是鞘氨醇-1-磷酸(sphingosine-1-phosphate, S1P)的转运蛋白，加强Spns2/S1P信号通路可以防止早期过度炎症反应和后期免疫抑制[31]. 针对脓毒症患者的免疫功能，对IL-7、粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor, GM-CSF)和PD-1/PD-L1等的研究为脓毒症免疫抑制的治疗提供新方法[6]. 此外, 对患者进行饮食干预、补充益生菌和FMT等措施能使患者体内肠道菌群的重组，作为新的治疗方法改善脓毒症患者的预后[107].

负性共刺激分子PD-1/PD-L1具有强大的免疫抑制作用，在淋巴细胞的功能障碍和凋亡中发挥重要作用[108]. 阻断PD-1/PD-L1的相互作用，可恢复淋巴细胞的正常功能, 增强机体的免疫应答, 提高脓毒症患者的生存率[109,110]. 阻断PD-1可上调CD86的表达和IFN-γ的产生, 激活耗竭的抗原提呈细胞和T细胞, 抑制IL-10的产生[111]. PD-1$^{-/-}$小鼠体内的促炎细胞因子IL-6, IL-10和TNF-α的表达水平增加[112]. 核转录因子红系2相关因子2(nuclear factor erythroid-2-related factor 2, Nrf2)是PD-L1的负调节因子，Nrf2可阻断PD-L1，改善脓毒症的免疫抑制 [113]. 目前针对PD-1/PD-L1通路治疗脓毒症免疫抑制的研究主要集中在体外实验和动物模型上, 人体的免疫系统和疾病过程远比实验环境复杂, 还需要更多的临床试验评估PD-1/PD-L1抗体在脓毒症患者中的安全性和有效性[48].

恢复正常的肠道菌群是脓毒症免疫抑制治疗的新靶点. FMT作为最近新兴的治疗技术可以增加机体内微生物的多样性并且恢复上皮的防御功能从而降低脓毒症患者的二次感染，逆转脓毒症免疫抑制的过程[114]. FMT可以减少肠道上皮细胞凋亡、改善黏液层的组成、上调肠道内紧密连接蛋白的表达、降低肠道通透性，缓解肠道炎症反应[115]. FMT和SCFAs的共同使用可以增加小鼠肠道内有益菌的丰度，使其恢复到与正常小鼠肠道内相同的水平[101]. FMT可减少精氨酸酶-1(Arginase-1，Arg-1)和活性氧(reactive oxygen species，ROS)的产生，降低MDSCs的免疫抑制功能, 并能促进MDSCs向巨噬细胞的转化[116]. FMT还可增加脓毒症小鼠结肠中膜整合蛋白Occludin的表达，下调NLRP3和GSDMD-N蛋白的表达，减少炎症因子IL-1β和IL-18的释放抑制细胞焦亡[101]，FMT治疗显著降低肠道中活化的caspase-3的表达，增加淋巴细胞的数量，降低机体IL-6和IL-10的水平[117]，从而改善脓毒症免疫抑制. 在脓毒症中, 某些病原体可直接抑制干扰素调节因子3(interferon regulatory Factor 3, IRF3), 而FMT可增加IRF3水平以恢复脓毒症患者的免疫功能[75]. FMT免疫抑制的调节也会相对加强脓毒症患者体内的某些炎症进程，因此有学者提出FMT对于重症监护病房(intensive care unit, ICU)中免疫功能低下的患者和重度脓毒症患者的治疗的安全问题[118]. 此外, 二甲双胍可增加肠道上紧密连接蛋白的表达，减轻肠道黏膜损伤，并影响肠道菌群的易感性，改善脓毒症患者的肠道菌群失调，用以治疗肠道渗漏[115]. 益生菌可重塑肠道微环境, 增加肠道内短链脂肪酸的含量, 并且降低肠道的PH值, 维持正常的肠道微环境[119]. 目前, 微生物组介导的治疗方法已经应用于脓毒症治疗[120].

4　总结

脓毒症是一种严重的全身性炎症反应，通常伴随着免疫系统的功能紊乱. 持续的免疫抑制可降低机体对感染源的控制能力，增加二次感染的风险. 而肠道菌群作为人体最大的微生物群落，在维持免疫稳态和防止感染方面起着至关重要的作用. 肠道菌群失调可通过多种途径调节脓毒症的免疫状态. 在治疗脓毒症时，除针对感染源和炎症反应进行治疗外，还应重视免疫状态的控制. 通过合理的饮食调整、FMT等措施, 可以改善肠道菌群失调, 改善免疫抑制状态, 提高脓毒症患者的治疗效果和预后.

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Sepsis immunosuppression and gut microbiota dysbiosis

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Prolonged immunosuppression in patients with late-stage sepsis is a key factor of their high mortality rate. Persistent immunosuppression is not only detrimental to the control of the original source of infection but also increases the risk of secondary infections by multidrug-resistant bacteria and opportunistic pathogens. Reversing the immunosuppressive state in sepsis patients is crucial for improving their survival rate. Gut microbiome dysbiosis can increase the susceptibility to sepsis through various mechanisms. This review aims to discuss the mechanisms of sepsis-induced immunosuppression and analyze the role of the gut microbiota, particularly its potential impact on the formation and progression of sepsis-induced immunosuppression.

sepsis, gut microbiota dysbiosis, immunosuppression

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