·专家论坛·

肠道菌群与加速康复外科:机制探索与临床转化新方向

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【摘要】 肠道菌群被誉为“被遗忘的器官”与“人类第二基因组”,是一个与宿主及外界环境紧密互作的复杂生态系统。近年发现肠道菌群与加速康复外科(enhanced recovery after surgery, ERAS)的临床效果密切相关。围手术期干预肠道菌群(如使用益生菌、合生元等)可改善手术预后,其核心机制涉及免疫调节、炎症调控、感染防控、营养代谢及肠道功能恢复五大方面。本文系统阐述了手术对肠道菌群的直接影响,深入剖析了上述五大作用机制,并结合最新研究,探讨了将肠道菌群调控整合于 ERAS 流程的新方向,包括个体化益生菌治疗、优化围手术期肠道准备、靶向调控术后炎症与肠道屏障等,旨在为未来机制深度探索与临床精准转化提供新思路。

【关键词】 肠道菌群;　加速康复外科;　机制;　临床转化

Gut microbiota and enhanced recovery after surgery: mechanistic exploration and new directions for clinical translation

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【Abstract】 The gut microbiota, hailed as the "forgotten organ" and the "second human genome", is a complex ecosystem that interacts closely with the host and the external environment. Recent findings suggest that the gut microbiota is closely associated with the clinical efficacy of enhanced recovery after surgery (ERAS). Perioperative interventions targeting the gut microbiota (*e.g.*, administration of probiotics and synbiotics) can improve surgical outcomes, and the core mechanisms involve five major aspects: immune regulation, inflammatory control, infection prevention and management, nutritional metabolism, and intestinal function recovery. This paper systematically elaborates on the direct impacts of surgery on the gut microbiota, analyzes the aforementioned five mechanisms in depth, and further explores new directions for integrating gut microbiota modulation into the ERAS protocol based on the latest research findings. These directions include personalized probiotic therapy, optimization of perioperative bowel preparation, and targeted regulation of postoperative inflammation and intestinal barrier function. The aim is to provide novel insights for in-depth exploration of underlying mechanisms and precise clinical translation in the future.

【Key words】 Gut microbiota;　Enhanced recovery after surgery;　Mechanism;　Clinical translation

加速康复外科(enhanced recovery after surgery, ERAS)是以循证医学证据为基础, 通过外科、麻醉、护理、临床营养等多学科协作优化围手术期临床路径,旨在缓解患者围手术期应激反应,从而减少术后并发症、缩短住院时间并促进康复[1]。经过多年的实践和发展,ERAS 理念现已广泛应用于多个外科领域[2-3]。肠道菌群被称为“被遗忘的器官”和“人类第二基因组”,构成复杂的微生态系统,参

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与多种肿瘤、代谢性疾病和免疫性疾病等的发生发展[4-5]。近年来,随着研究的深入,肠道菌群被发现与 ERAS 也密切相关,可在多种 ERAS 干预措施中发挥中介作用,调节人体代谢和炎症反应。围手术期改变肠道菌群(如使用益生菌和合生元),可带来更好的手术效果,包括降低感染风险、减轻炎症反应及加快肠道功能恢复[6]。同时,ERAS 措施本身也可通过减轻围手术期应激反应来影响患者肠道菌群的组成与功能[7]。本文系统阐述了肠道菌群与 ERAS 的研究进展,以期在未来机制探索与临床转化方面提供一定的思路。

1 手术对肠道菌群的直接影响

手术是 ERAS 实施的核心环节,可显著改变肠道菌群结构[8]。Žukauskaitė等[9]研究发现,根治性胃切除术可导致拟杆菌门和变形杆菌门的丰度增加,厚壁菌门和放线菌门的丰度减少,并出现口腔相关细菌(如埃希菌属、志贺菌属、马链球菌、不可培养的链球菌和肠杆菌科细菌等)的富集。Christodoulidis 等[10]则发现,与未行胃切除手术者相比,行胃切除的患者术后炎症性肠病发病率升高,远端胃肠道常定植链球菌属、韦荣氏球菌属、普雷沃氏菌属、口腔杆菌属和艰难杆菌属等口腔细菌,其丰度可达未行胃切除手术者的 2.5~4.0 倍。一项系统评价结果显示,胃癌患者术后肠道菌群 β 多样性下降、有益菌减少,这些变化与术后炎症反应和并发症风险密切相关[11]。

在结直肠癌手术中,Deng 等[12]发现,患者术后的拟杆菌门和厚壁菌门显著减少,而变形菌门则明显增加。Ohigashi 等[13]的研究则显示,结直肠癌术后患者的专性厌氧菌(如球状梭菌群、脆弱拟杆菌群、普雷沃氏菌属和双歧杆菌等)减少,而兼性厌氧或需氧菌(如肠杆菌科、肠球菌属、葡萄球菌属和假单胞菌属等)则相对富集。此外,上、下消化道手术对肠道菌群谱的影响也存在差异。例如,全胃切除术后行 Roux-en-Y 吻合患者的普雷沃氏菌属与拟杆菌属的比值升高,而在右半结肠切除术后患者中,该比值则降低[14]。

综上,手术对肠道菌群具有直接影响,且这一改变因疾病种类、手术方式及部位而异,胃肠道手术对肠道菌群的影响尤为显著。术后合理补充有益菌,优化肠道菌群结构,可能有助于加速患者康复。

2 肠道菌群影响术后康复的五大机制

2.1 免疫调节:术后防御的利器

良好的免疫功能是患者术后康复的基础。肠道菌群的失衡可影响肠道屏障完整性和宿主免疫功能。菌群发酵代谢产物短链脂肪酸(short-chain fatty acids, SCFAs,主要包括乙酸、丙酸和丁酸)可与 G 蛋白偶联受体-43 相互作用或抑制组蛋白去乙酰化酶,调节 1 型辅助性 T 细胞(helper T cell, Th 细胞)及细胞毒性 T 淋巴细胞功能,发挥免疫调节作用。直接补充膳食纤维和益生菌,或通过粪菌移植改变肠道菌群结构,既能提高 SCFAs 水平,又能抑制肿瘤的发展[15]。McBride 等[16]发现,SCFAs 中的丁酸可显著抑制 Th17 细胞相关因子视黄酸受体相关孤儿受体(retinoic acid receptor-related orphan receptors, ROR)γt 和白介素(interleukin, IL)-17,同时上调调节性 T 细胞标志分子 FOXP3,参与自身免疫调节。Yang 等[17]研究显示,肠道载脂蛋白 L9a/L9b 可靶向调节拟杆菌,诱导其释放外膜囊泡,增强宿主的 γ 干扰素信号转导,促进肠上皮细胞中主要组织相容性复合体Ⅱ类的表达,从而维持免疫稳态。菌群代谢物 L-硒代蛋氨酸也能有效增强 $CD8^+$ T 细胞的效应功能[18]。

Zheng 等[19]研究显示,益生菌混合物可增强胃癌切除术后患者的免疫力,减轻炎症,促进菌群恢复与术后康复,这一结果在大鼠模型中也得到证实。另有研究表明,危重症患者在治疗上辅以益生菌、益生元或粪菌移植,有助于维持肠道屏障、调节免疫反应,减少脓毒症或急性呼吸窘迫综合征等术后并发症的发生[20]。结直肠癌患者术前口服双歧三联活菌,可提高免疫球蛋白 G 和分泌型免疫球蛋白 A 水平,减少术后炎症与并发症的发生,其机制可能与维持菌群稳定、限制细菌移位、增强免疫功能及降低全身应激反应有关[21]。因此,科学应用益生菌或其代谢产物可调节机体免疫,促进患者康复。但如何针对特定疾病或手术方式实现精准菌属或代谢产物的干预,仍需更多研究证据。

2.2 炎症调控:平衡修复与损伤

手术应激引发的过度炎症反应会导致免疫功能障碍,增加感染风险并延迟恢复。而肠道菌群代谢产物丁酸盐可抑制促炎性细胞因子并上调抗炎细胞因子,发挥炎症调控的作用[15]。Kotzampassi 等[22]研究显示,结直肠癌患者围手术期口服益生菌,可通

过细胞因子信号转导抑制因子 3 降低肿瘤坏死因子(tumor necrosis factor, TNF)、IL-6 等促炎性细胞因子的表达。行胃切除术的患者在围手术期口服益生菌混合物可减轻炎症反应，稳定微生物多样性[23]。Cao 等[24]研究则发现,丁酸梭菌可显著降低胃癌患者术后的炎症水平,提升免疫功能,增加有益菌(如拟杆菌属、粪杆菌属和吉米菌属等)丰度,降低致病性菌(如链球菌属、脱硫弧菌属和放线菌属等)丰度,并显著上调 SCFAs(包括乙酸、丙酸、丁酸和异丁酸) 水平。另有一项随机对照试验显示，口服益生菌混合物可减少结直肠癌患者术后促炎性细胞因子(如 TNF-α、IL-17A、IL-17C、IL-22 和 IL-12)的产生,预防术后并发症[25]。

益生元、益生菌和合生元均具有抗炎作用,并能改变微生物组，其中合生元及发酵食品的抗炎作用可能更强。即使是短期的围手术期菌群预康复治疗,也可能显著改善手术结局[26]。因此,在围手术期补充这些制剂对维持菌群稳定、促进康复具有临床价值,但其深层作用机制仍有待阐明。

2.3 感染防控:肠道屏障与全身防御

术后感染是重大健康负担,腹部手术部位感染的发生率远高于其他类型的手术,可达 15%~25%[27]。一项 Meta 分析表明，结直肠癌患者围手术期给予益生菌/合生元可显著降低感染、败血症和腹泻发生率，加快肠道功能恢复，缩短抗生素使用时间[28]。Iliev 等[29]研究发现,短乳杆菌 DPL5 能产生破坏金黄色葡萄球菌等病原体生物膜形成的杀菌化合物。约氏乳杆菌 L531 可通过调节内质网应激、线粒体自噬和 NOD 信号转导等通路，恢复菌群平衡、维持 SCFAs 水平和调节免疫反应,有效预防沙门氏菌感染[30]。一项系统评价研究结果显示,益生菌/合生元可有效降低肝移植患者的总体感染率,其作用可能与改善肠道屏障功能、恢复肠道菌群及减轻炎症有关[31]。Huang 等[32]发现,全肠外营养会降低鼠乳杆菌的丰度，补充鼠乳杆菌可促进肠道上调吲哚-3-羧酸,激活核受体 RORγt,刺激 3 型天然淋巴样细胞分泌 IL-22,从而加强肠道屏障的完整性,降低感染易感性。

围手术期使用益生菌和/或合生元可通过提升有益菌的水平、强化肠道屏障、减轻氧化应激及促进抗炎 SCFAs 产生,降低感染风险[31,33]。未来需要更深入的研究以确定最有效的菌株并评估其在不同患者群体中的预防效果。

2.4 营养代谢:术后能量供给的核心角色

营养治疗是 ERAS 的核心要素之一。营养不良是术后严重并发症的独立危险因素,中度和重度营养不良患者的严重并发症发生风险分别增加近 15 倍和 20 倍,并影响总生存[34-35]。研究显示,肠道菌群代谢产物 SCFAs 可通过调节组蛋白去乙酰化酶 3-H3K27ac-过氧化物酶体增殖物激活受体 γ 轴进而调控脂肪酸和甘油三酯转运,并作用于 CD36,影响胰岛素靶器官对胰岛素的敏感性[36]。Chen 等[37]研究发现,副干酪乳杆菌 ZFM54 不仅能提高酸奶的酸度、持水量和活乳酸菌数量,还能增加有益代谢物如 N-乙基甘氨酸和 L-赖氨酸的含量。

总之，肠道菌群及其代谢产物在营养代谢调控中发挥关键作用。口服益生菌有助于维持肠道稳态、促进营养吸收,但其个体化应用方案仍需更多研究来确定。

2.5 肠道功能:吻合口愈合与胃肠动力

吻合口漏是消化道手术的严重并发症，影响患者术后康复,并可危及生命[38-39]。影响吻合口愈合的因素众多,如浆膜层缺失、肌纤维纵向方向和组织缺血等[40]。近年的研究发现,肠道菌群与吻合口愈合密切相关，是吻合口并发症的关键驱动因素。粪肠球菌和铜绿假单胞菌在术后吻合口组织中富集,可溶解胶原蛋白并激活其他酶解途径,破坏结缔组织[41]。因此,个体化调节微生物组可能有助于降低吻合口漏风险。van Praagh 等[42]研究发现，结直肠吻合口漏患者菌群中普雷沃氏菌属和链球菌属相对较少,而毛螺菌科、布劳特氏菌属和拟杆菌科则相对较多。Shogan 等[43]研究发现,粪肠球菌可通过降解胶原蛋白和激活宿主肠道组织中的基质金属蛋白酶 9 (matrix metalloproteinase-9, MMP9)参与吻合口漏的发生;直接外用抗生素或抑制 MMP9 可预防大鼠吻合口漏，而静脉注射抗生素则效果有限。

术后胃肠道功能障碍(postoperative gastrointestinal dysfunction, POGD) 是胃肠道手术的常见并发症,在结直肠手术中的发生率为 4.5%~42.7%[44]。肠道菌群改变会促进 POGD 发生。研究表明,术后肠梗阻患者拟杆菌属、副拟杆菌属和瘤胃球菌属的丰度增加[45]。Shanahan 等[46]研究显示,十二指肠中的链球菌属、普雷沃氏菌属和韦荣氏球菌属等丰度与胃排空时间呈负相关。Lötstedt 等[47]研究则发现，术后出现胃排空延迟患者的胃部微生物 α 多

样性显著降低。

菌群失调与脑-肠轴改变相关，也是胃瘫和功能性消化不良等疾病的发病基础。益生菌可能通过影响激素和 5-羟色胺分泌、肠道黏膜屏障、肠神经系统和肌层巨噬细胞等机制改善胃排空，可作为促进术后肠道功能恢复的潜在干预措施[48-49]。

3 肠道菌群与 ERAS 结合的临床转化新方向

3.1 迈向个体化益生菌治疗

不同疾病类型或手术方式下的肠道菌群分布不同，益生菌疗效亦存在差异，需为患者制定个体化方案。研究显示，与进行常规肠内营养治疗相比，术后联用双歧杆菌可缩短胃癌患者的康复时间，改善免疫与营养状况[50]。而结直肠癌术后患者口服多菌株益生菌混合物(包含嗜酸乳杆菌、干酪乳杆菌、植物乳杆菌、鼠李糖乳杆菌、乳酸双歧杆菌、两歧双歧杆菌、短双歧杆菌和嗜热链球菌等)可降低术后并发症的发生率[51]。多菌株益生菌(包含两歧双歧杆菌、乳酸双歧杆菌、屎肠球菌、嗜酸乳杆菌、鼠李糖乳杆菌、乳酸乳球菌等)还能改善结肠镜检查后的胃肠道问题，如缩短便秘天数，减轻腹痛、腹胀、腹泻等症状等[52]。一项大鼠模型研究表明，结肠手术后补充合生元(含有戊糖片球菌、肠膜明串珠菌、副干酪乳杆菌、植物乳杆菌、菊粉、燕麦麸、果胶和抗性淀粉)和谷胱甘肽可增加结肠吻合口的机械强度，从而提高抗破裂的耐受力，减少或消除吻合口裂开，并限制细菌易位[53]。还有 Meta 分析显示，围手术期使用益生菌(单株或多株联合使用)或合生元可显著降低肝脏手术后感染发生率，缩短抗生素治疗时间[54]，对结直肠癌患者也有类似益处[55]。

未来需深入研究以明确不同菌属的疗效，为精准选菌提供依据。多菌株联用的价值已得到证实，但其是否优于单菌株仍需更多证据支持。菌株选择、剂量及时机等参数也值得进一步探讨。

3.2 优化围手术期肠道准备策略

传统机械性肠道准备(联合口服抗生素)可能改变菌群并增加感染风险，在 ERAS 背景下已非常规操作[56-57]。一项随机对照试验结果显示，肠道准备会降低菌群丰度和多样性，且菌群难以在短期内恢复至肠道准备前的水平[58]。

应对策略方面，结肠镜检查前 1 个月口服益生菌有助于肠道准备后菌群的快速恢复，并减少相关并发症[59-60]。联合不可溶性膳食纤维和益生菌进行肠道准备，可减少聚乙二醇用量并保持肠道清洁质量，改善患者耐受性[61]。未来方向应从单纯“肠道清洁”转向兼顾菌群调控的“菌群准备”。

3.3 靶向调控术后炎症与肠道屏障功能

术后炎症反应和肠道屏障功能受损是影响患者术后康复的重要因素之一，益生菌/合生元的使用有助于改善相关问题。一项 Meta 分析显示，补充合生元和益生元有助于改善成人炎症反应，且合生元的作用更为显著[62]。Fu 等[63]研究发现，口腔牙槽骨术后口服补充罗伊氏乳杆菌可降低促炎性细胞因子(IL-1β、IL-6 和 TNF-α)水平，减轻炎症并增强牙槽骨稳定性。肝切除术患者围手术期使用益生菌可降低术后感染性并发症的发生率，以及血清内毒素水平和白细胞计数[64]。结直肠癌术后患者使用益生菌可降低血浆内毒素、胰岛素样生长因子 1 的浓度，以及 D-乳酸、尿乳果糖/甘露醇比值水平，改善术后肠道屏障功能，促进术后早期炎症反应的恢复[65]。Kim 等[66]在豚鼠术后肠梗阻模型的研究中发现，益生菌的使用可降低其术后肠梗阻的肠道通透性，减轻炎症反应，这为术后肠梗阻的管理提供了一种潜在的治疗方法。

总的来说，益生菌在减轻术后炎症、恢复肠道屏障功能等方面具有潜力，但需根据菌种和疾病特异性开展更多研究以优化疗效。

3.4 未来研究方向

针对肠道菌群在围手术期的应用，未来研究可聚焦于以下几个方面。①整合多组学数据：结合宏基因组与代谢组学，构建个体化数据库，发现关键生物标志物(如肠道菌群代谢物苯乙酰谷氨酰胺被证实与免疫治疗反应呈负相关[67])。②深化机制探索：利用动物模型与单细胞测序等技术，解析菌群-宿主相互作用的新通路。③推动高质量临床转化：开展多中心随机对照试验，验证菌群导向 ERAS 策略的普适性与有效性，并探索开发包含特定益生元/益生菌的特殊医学用途配方食品，最终建立“微生物组-外科”精准医疗模式。

4 总结

ERAS 理念与肠道菌群研究的融合，正推动围手术期管理从宏观流程优化向微观机制干预的深刻变革。手术直接影响菌群，而菌群通过免疫、炎

症、感染、营养、肠道功能五大机制反作用于术后康复进程。通过发展个体化益生菌治疗、优化肠道准备、靶向调控炎症与肠道屏障等新策略,有望实现更精准的围手术期管理。未来需围绕“个体化+机制探索”双主线,通过高质量研究推动两者深度融合,最终实现患者快速康复与生存质量提升。

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·最新研究速递·

仑伐替尼联合经导管动脉化疗栓塞及程序性死亡受体 1 抑制剂用于不可切除中晚期肝细胞癌的转化治疗:一项Ⅱ期试验及探索性生物分子研究

Lenvatinib plus transarterial chemoembolization and PD-1 inhibitors as conversion therapies for unresectable intermediate-advanced hepatocellular carcinoma: a phase Ⅱ trial and exploratory biomolecular study

【摘要】 对于不可切除的中晚期肝细胞癌,转化治疗是实现根治性切除的重要途径。本研究旨在比较联合仑伐替尼、经导管动脉化疗栓塞(transcatheter arterial chemoembolization, TACE)和程序性死亡受体 1(programmed death-1, PD-1)抑制剂的 LEN-TAP 方案与单纯 TACE 的治疗效果。研究主要终点为挽救性肝切除率, 次要终点包括客观缓解率(objective response rate, ORR)、总生存(overall survival, OS)期、无事件生存(event-free survival, EFS)期、无复发生存(recurrence-free survival, RFS) 期及安全性评估。2020 年 10 月至 2021 年 11 月,142 例符合条件的受试者被随机分配至 LEN-TAP 组(71 例)或单纯 TACE 组(71 例)。中位随访 24.2 个月时,LEN-TAP 组的挽救性肝切除率(59.2%比 18.3%,P<0.001)和 ORR(78.9%比 16.9%,P<0.001)均高于单纯 TACE 组。LEN-TAP 组的中位 OS 期、EFS 期和 RFS 期也延长(OS 期:未达到比 23.0 个月,P<0.001;ESF 期:20.03 个月比 6.52 个月,P<0.001;RFS 期:36.6 个月比 19.0 个月,P=0.048)。尽管 LEN-TAP 组 3 级治疗相关不良事件发生率较高(60.6%比 21.1%,P<0.001),但未出现 4 级及以上不良事件。通过探索性生物分子分析,研究团队发现外周血中 HLA-DR$^+$CD38$^+$CD8$^+$ T 细胞水平升高与治疗反应改善相关, 可能作为预测疗效的潜在生物标志物。综上,LEN-TAP 方案是一种高效、安全的肝细胞癌治疗策略,为中晚期肝细胞癌患者提供了新的治疗选择,并为筛选获益人群提供了新的免疫学标志物依据。

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