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阑尾对肠道微生物组和结直肠癌的影响

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摘　要

阑尾切除术在结直肠癌(CRC)发病机制中的作用是近期争议的焦点。鉴于阑尾切除术仍是最常见的外科手术之一，也是急性阑尾炎的一线治疗策略，阐明既往阑尾切除术与后续结直肠癌发生之间的关联具有重要的临床意义，因其可能产生远期健康影响。本综述旨在整合阑尾切除术后患者结直肠癌相关性的研究证据，探讨微生物组在阑尾切除术与结直肠癌发病机制中的潜在作用，并对当前关于阑尾功能的认知进行评估。

关键词

阑尾切除术，阑尾，结直肠肿瘤，胃肠道微生物组

The Impact of the Appendix on Intestinal Microbiome and Colorectal Cancer

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Abstract

The potential association between appendectomy and colorectal cancer (CRC) pathogenesis has emerged as a subject of ongoing scientific debate. Given that appendectomy remains one of the most prevalent surgical procedures worldwide and constitutes the first-line therapeutic intervention for acute appendicitis, elucidating the causal relationship between prior appendectomy and subsequent colorectal carcinogenesis carries substantial clinical implications due to its potential long-term health consequences. This systematic review seeks to synthesize existing evidence regarding

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CRC susceptibility in post-appendectomy cohorts, investigate the potential mediating role of microbiome dysbiosis in appendectomy-associated CRC pathogenesis, and reassess current perspectives on the appendix's immunological functions through the lens of oncogenic transformation.

Keywords

Appendectomy, Appendix, Colorectal Cancer, Intestinal Microbiome

1. 前言

结直肠癌(CRC)是全球第三大常见恶性肿瘤，在发展中国家与发达国家的癌症相关死亡率中均占据重要且持续增长的地位[1]。尽管遗传因素在 CRC 发生发展中具有重要作用，但环境暴露与生活方式亦构成其风险体系的重要组分[2]。阑尾炎作为急腹症的常见病因，其终生发病风险约为 7%~8%，不仅在发展中国家导致大量的死亡和生存时间减少，在发达国家与发展中国家均构成急诊就诊的重要诱因[3]。鉴于传统观点将阑尾视为退化残余器官且认为其功能缺失，加之阑尾切除术长期作为阑尾炎一线治疗方案，该术式在 CRC 发病机制中的作用已成为近期学术争议的焦点。现行外科指南仍推荐阑尾切除术作为多数阑尾炎病例的首选治疗策略，但近年来抗生素保守治疗已被证实可作为有效替代方案，尤其适用于无并发症的单纯性阑尾炎(无蜂窝织炎、脓肿、穿孔或阑尾石)患者[4]。即便抗生素治疗成功者，限期阑尾切除术仍被视为根治性治疗及降低复发风险的重要手段[5]。作为临床开展最为广泛的外科术式之一，阐明阑尾切除术与 CRC 发生之间的潜在关联具有重要临床价值，因其可能对患者长期健康结局产生深远影响。

本综述系统整合阑尾切除术后 CRC 关联性的循证医学数据，深入探讨肠道微生物组在阑尾切除术与 CRC 发病机制中的交互作用，并对当前阑尾生理功能的认知体系进行深入评估。

2. 阑尾切除术后微生物组失调

Sanders 等[6]针对艰难梭菌性结肠炎的研究首次提出阑尾可能作为肠道共生菌的“安全港”，但其调节功能在抗生素干预后可能失效。后续研究[7]进一步证实，阑尾切除术后患者艰难梭菌感染预后更差，提示菌群稳态破坏可能介导此现象。Cai 等[8]通过病例对照研究发现，阑尾切除术显著改变肠道菌群结构：术后人群埃希氏菌、志贺氏菌、韦荣球菌、克雷伯菌、巨球形菌、黄杆菌及链球菌丰度升高，而罗斯氏菌、巴恩斯氏菌、丁酸球菌、气味杆菌及丁酸单胞菌等保护性菌属显著减少。值得注意的是，术后菌群紊乱呈现时间依赖性，术后 2 年以上患者菌群组成逐渐恢复至术前状态，这与 Wu 等[9]及 Lee 等[10]关于术后 CRC 风险时相性变化(术后早期风险升高，随时间推移递减)的发现相契合，提示术后早期可能为益生菌或粪菌移植干预的潜在时间窗。但需指出，此类回顾性研究可能存在监测偏倚(术后结肠镜筛查频率增加或导致早期 CRC 检出率升高)。

Shi 等[11]系统阐明了阑尾切除术诱导的菌群双相改变：促癌菌群(普通拟杆菌、脆弱拟杆菌、小韦荣球菌、反刍普雷沃菌、深褐普雷沃菌、齿普雷沃菌及丹氏普雷沃菌)显著富集，而保护性菌种(Blautia sp. SC05B48、产气柯林斯菌、Choco86 毛螺菌科细菌、海氏肠球菌及 YL58 Blautia 菌)显著耗竭。两组菌群形成互斥性生态网络，且伴随肠道屏障功能损伤(E-钙黏蛋白及黏附连接蛋白表达下调)，与前述机制研究

互为印证。

Bollinger 等[12]进一步揭示了阑尾与近端结肠生物膜稳态维持的关联，提出阑尾切除术后近端结肠生物膜失调可能尤为显著，这为右半结肠癌发病率升高的临床现象提供了潜在解释。但该假说尚需直接实验证据支持。

3. 微生物组在 CRC 发病机制中的核心作用

目前关于阑尾功能及其切除术后结直肠癌(CRC)发病率升高的研究，主要围绕“阑尾切除术引发肠道微生物组紊乱”的假说展开。由于肠道微生物组直接影响上皮细胞增殖分化、肠道免疫稳态及其与菌群构成的动态互作，研究指出此类生理参数的异常可能通过诱导免疫调节失调最终促进肿瘤发生[13]。

结直肠癌(CRC)的发病机制长期被认为与肠道菌群丰度改变(即菌群失调)存在关联。研究表明，CRC 患者肠道微生物组成呈现整体性偏移，反映其肠道生态微环境紊乱，表现为致病菌属丰度升高而保护性菌属丰度降低。最近的一篇综述系统总结了参与此生态转变的关键菌种：CRC 患者粪便及肿瘤样本中除了埃希氏菌–志贺氏菌属，脆弱拟杆菌、具核梭杆菌、米氏小单胞菌、溶糖卟啉单胞菌、中间普雷沃氏菌等显著富集[14]-[16]；而具有保护作用的丁酸梭菌、嗜热链球菌及厚壁菌门成员则在 CRC 样本中丰度显著降低[15]-[17]。

值得注意的是，此类肠道菌群特异性改变模式亦见于长期吸烟及酗酒等高危人群，而终止此类致癌危险因素后保护性菌群丰度可恢复至正常水平，提示生活方式干预可能逆转菌群失调状态[18]-[20]。上述发现为阐明菌群失调在 CRC 发生中的生物学作用提供了理论依据。

肠道生物膜是肠道微生物组概念的延伸结构，特指由胞外聚合物(EPS)构成的三维黏液网络，其整合了定植菌群及其代谢产物(如脂类、多糖、蛋白质、核酸及离子)，在维持肠道免疫调节、屏障功能及细胞信号传导中发挥关键作用[21]。

近期研究显示，右半结直肠癌(CRC)肿瘤及腺瘤样本中细菌生物膜阳性率显著高于左半病变[22]。此类生物膜阳性肿瘤伴随 E-钙黏蛋白表达缺失(该分子参与细胞间黏附并调控膜通透性)，同时 IL-6/STAT3 信号通路异常激活，可能通过促进细胞增殖并抑制凋亡驱动肿瘤发生。Sobhani 等[23]进一步发现 CRC 患者 IL-17 阳性细胞数量增加，且与拟杆菌属(已知促癌菌属)定量负荷显著相关，这与 Sears 与 Pardoll 提出的“α-致病菌”理论一致：产肠毒素脆弱拟杆菌可通过激活 STAT3，进而诱导 IL-17/IL-23 信号级联反应，促进慢性炎症及肿瘤细胞存活[24]。

最新研究还揭示特定条件致病菌(如粪肠球菌、侵袭性大肠杆菌)具有直接遗传毒性。这些菌株可诱导染色体不稳定性，并分泌聚酮肽类基因毒素 colibactin，激活 p53 表达并促进肿瘤细胞增殖[25]。E-钙黏蛋白介导的屏障功能破坏促使共生菌及其代谢产物浸润至肿瘤间质，通过“驱动–乘客”协同模型加剧肿瘤相关炎症。此外，肿瘤微环境中巨噬细胞、树突状细胞、自然杀伤细胞及中性粒细胞产生活性氧(ROS)，进一步诱导 DNA 损伤[26]。值得注意的是，这些促癌菌群在 CRC 患者中呈现选择性富集，提示可能存在肿瘤发生的正向反馈环路。

上述多因素共同构建了以肠道菌群原发性失调为核心的 CRC 发病机制模型，涉及菌群结构紊乱、生物膜形成、免疫调控异常及遗传毒性效应等多重通路交互作用。

4. 既往阑尾切除术与 CRC 关系的流行病学观察

目前相关的研究对于阑尾切除术后对 CRC 风险变化的影响尚存在争议。多项研究提示阑尾切除术后 CRC 风险呈上升趋势。Wu 等[9]与 Shi 等[11]发现，老年患者(分别定义为手术时年龄 ≥50 岁及≥60 岁)的 CRC 风险增幅更为显著，HR 分别为 2.02 (95% CI: 1.71~2.40)和 1.24 (1.06~1.45)。Wu 等[9]与 Lee 等[10]

指出，CRC 风险在术后前 3 年达到峰值，随后逐渐恢复基线水平。值得注意的是，Wu 等[9]发现因其他手术附带行阑尾切除的患者 CRC 风险最高(HR = 2.90, 95% CI: 2.24~3.75, P < 0.001)。Song 等[27]的研究虽未发现整体风险升高，但亚组分析显示术后 5~14 年患者的 CRC 风险显著增加(HR = 1.12, 1.05~1.20)，而术后 1~4 年组未观察到风险变化(HR = 1.05, 0.94~1.17)，此结果与前述研究存在矛盾。

Mandi 等[28]的病例对照研究未发现术后 CRC 风险显著增加。Rothwell 等[29]则提示阑尾切除术可能降低结肠癌(排除直肠癌)风险(HR = 0.90, 0.81~0.99)，尤其远端结肠癌风险下降更显著(HR = 0.77, 0.65~0.90)，但全人群分析未达统计学显著性。vandenBoom 等[30]的研究显示，术后全癌种风险降低(HR = 0.86, 0.75~0.98, P = 0.005)，其中结肠癌风险降幅尤为明显(HR = 0.65, 0.43~0.97)，且术后前 4 年仅 3 例恶性肿瘤发生。Cope 等[31]针对儿童群体的队列研究亦未发现术后总体癌症或结肠癌风险增加，但提示青少年期(15~19 岁)行阑尾切除术者胃癌风险显著升高。

Liu 等[32]的最新系统综述与荟萃分析显示，术后人群 CRC 合并比值比(OR)为 1.31 (1.05~1.62)。地理分层分析表明，该风险在美洲(OR = 1.68, 1.15~2.44)及亚洲人群(OR = 1.46, 1.04~2.05)中显著，而欧洲人群无统计学差异(OR = 0.94, 0.87~1.02)。作者将这种地域差异归因于社会经济水平及结直肠癌筛查普及度差异。

根据国际共识[33]，左半结直肠癌定义为起源于左结肠(脾曲)以远肠段的恶性肿瘤，包括降结肠、乙状结肠及直肠；右半结直肠癌则指源自左结肠曲近端肠段(盲肠、升结肠及横结肠)的肿瘤。现有证据表明，左右半结直肠癌在分子特征与临床病理学行为上存在显著异质性[34] [35]。具体而言，右半结直肠癌更易呈现 BRAF 基因突变及错配修复缺陷/微卫星高度不稳定(dMMR/MSI-H)表型，而左半肿瘤则多伴随 APC、KRAS 及 p53 基因突变[36]-[38]。有 3 项研究[11] [27] [39]均提示阑尾切除术后患者右半结直肠癌发病率显著增加，其中 Song 等[27]研究发现该趋势在术后 5~14 年尤为显著。这一发现具有重要临床意义，因既往研究已证实右半结肠癌患者总体预后较左半更差[40] [41]。尽管该现象的潜在机制尚未阐明，结合文献报道的左右半结直肠癌驱动基因突变谱差异，推测阑尾切除术可能通过调控特定驱动突变(尤其是右半结肠癌特征性突变)参与致癌过程。

5. 阑尾生理功能的重新评估

人类阑尾长期以来被视为进化残留器官，但其潜在免疫学功能及对肠道有益菌群的调控作用逐渐受到关注。比较解剖学研究表明，草食性哺乳动物的阑尾显著长于肉食性动物，可能与其作为纤维素分解菌的发酵腔室有关；而包括类人猿在内的杂食或肉食动物阑尾常缺如或退化，提示其在消化系统中的生理作用有限[42]。尽管如此，多项研究证实阑尾具有重要免疫学功能：其富含肠道相关淋巴组织(GALT)及共生菌生物膜[12] [43]，是 IgA 分泌的主要部位[44] [45]，并可能作为肠道菌群储备库，在病原体感染后介导菌群快速重建[12]。进化生物学研究显示，阑尾的独立进化与哺乳动物寿命延长相关[42] [46]支持其在维持菌群免疫平衡中的核心作用。临床观察亦发现阑尾切除术与溃疡性结肠炎、类风湿关节炎等免疫性疾病风险改变相关[47] [48]。

最新研究进一步揭示阑尾对结肠免疫功能的调控机制。阑尾切除术可降低溃疡性结肠炎发病风险及结肠切除率，可能与 $\alpha 4\beta 7$ 整合素介导的淋巴细胞归巢功能受损有关[49]。免疫组化分析显示，术后肠道 $CD3^+$、$CD8^+$ T 细胞浸润显著减少，且 $CD4^+/CD8^+$ T 细胞 PD1 表达下调，效应记忆 T 细胞与中枢记忆 T 细胞比例失衡[50]。结合术后右半结肠癌(MSI-H/dMMR 亚型为主)发病率升高及拟杆菌、普雷沃菌、梭杆菌等促癌菌群富集的发现[11] [38] [51]，推测阑尾切除术通过改变近端结肠免疫微环境(如削弱抗肿瘤免疫监视)，协同菌群失调共同促进肿瘤发生。

基于上述证据，临床需重新评估急性阑尾炎治疗策略。2020 年世界急诊外科学会(WSES)指南推荐无

并发症(无阑尾石)患者可优先选择抗生素非手术治疗[52]但需警惕其并发症及复发风险[53]-[55]。值得注意的是，阑尾炎可能为早期 CRC 的继发表现(如癌前病变阻塞阑尾腔) [56]-[59]，部分研究提示急性阑尾炎患者后续结肠癌风险升高，可能与隐匿性肿瘤相关[60] [61]。因此，临床决策需权衡手术干预(根治潜在癌变)与器官保留(维持菌群–免疫稳态)的利弊，实施个体化诊疗方案。

当前关于阑尾–菌群-CRC 轴的研究仍处于探索阶段，现有证据尚不足以指导临床实践。但可明确的是，阑尾绝非功能冗余器官，其在肠道菌群动态平衡及疾病发生中扮演复杂角色。随着技术的进步，阑尾在结直肠癌发生中的生物学意义或将迎来突破性认知。

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