

肠道菌群与胃肠道恶性肿瘤关系的研究进展

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摘 要

肠道微生物群是人体微生物生态系统的重要组成部分, 与宿主的免疫防御和代谢活动密切相关。近期研究显示, 肠道微生物群与胃肠道癌症的发生发展有着复杂的相互作用。本文综合分析了肠道菌群与胃癌、结直肠癌之间的关系, 探讨了菌群失衡如何影响肿瘤的发病机制, 并评估了菌群调节在预防和治疗胃肠道肿瘤中的潜在应用。本综述旨在为深入理解胃肠道肿瘤的发病机制和开发新的防治策略提供科学依据。

关键词

肠道菌群, 胃肠道恶性肿瘤, 菌群失衡, 预防, 治疗

Research Progress on the Relationship between Intestinal Flora and Gastrointestinal Malignancy

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Abstract

The gut microbiota is an important component of the human microbial ecosystem and is closely related to the immune defense and metabolic activities of the host. Recent studies have shown complex interactions between the gut microbiota and the occurrence and development of gastrointestinal cancers. In this paper, we comprehensively analyzed the relationship between the intestinal flora and gastric cancer and colorectal cancer, explored how the flora imbalance affects the pathogenesis

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of tumors, and evaluated the potential application of flora regulation in the prevention and treatment of gastrointestinal tumors. This review aims to provide a scientific basis for deeply understanding the pathogenesis of gastrointestinal tumors and developing new prevention and control strategies.

Keywords

Intestinal Flora, Gastrointestinal Malignancy, Flora Imbalance, Prevention, Treatment

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1. 前言

肠道微生物群，常被称作人体的“第二基因组”，在维持人体健康方面发挥着至关重要的作用。肠道菌群与胃肠道恶性肿瘤关系密切，其组成变化与肿瘤的发生、发展及治疗反应显著相关。研究表明[1][2]，肠道菌群通过慢性炎症、代谢产物产生等途径促进胃癌和结直肠癌，例如，幽门螺杆菌感染与胃癌风险增加有关，而某些益生菌可能通过增强黏膜屏障和调节免疫反应来抑制肿瘤发展[3]。此外，肠道菌群还能通过影响药物疗效、消除抗癌作用和介导毒性作用，在抗癌治疗反应中发挥作用[4][5]。

尽管目前对于肠道微生物群与胃肠道肿瘤关系的研究取得了一定的进展，但仍有许多未知的领域等待探索，未来的研究需要进一步阐明肠道微生物群影响肿瘤发生的具体机制，以及如何通过调节肠道微生物群来预防和治疗胃肠道肿瘤。随着研究的深入，基于肠道微生物群的肿瘤治疗策略有望成为未来肿瘤治疗的新方向。

2. 背景介绍

2.1. 胃肠道肿瘤的现状

2.1.1. 胃癌的流行病学与病理机制

胃癌是全球范围内最常见的恶性肿瘤之一，尤其在东亚地区，包括中国，其发病率和死亡率均居高不下，据2020年统计，中国胃癌新发病例和死亡病例分别占全球的44%和48.6%，男性患病率高于女性[6]。研究表明，现代生活中的饮食习惯改变、体重超标、吸烟、过度饮酒以及胃肠道炎症等行为模式与肿瘤风险紧密相关[7]。肠道菌群中幽门螺杆菌(*Helicobacter pylori*)感染是胃癌的主要危险因素，此外遗传因素、出生季节、吸烟以及其他肠道菌群失衡，可能与胃癌的相关性，也引发了科学家的深入探究[8][9]。胃癌根据解剖位置可分为贲门型和非贲门型，根据组织学特征可分为肠型、弥漫型和混合型。肠型胃癌通常与幽门螺杆菌感染有关[10]，而弥漫型胃癌则与慢性炎症相关，Sasaki Akiko等研究者[11]发现结节性胃炎患者的胃窦和胃体中诱导了涉及多个肿瘤抑制基因的严重异常甲基化，这与其较高的胃癌风险相一致，且预后相对较差。随着对胃癌病理机制的深入研究，分子靶向治疗和免疫治疗为胃癌治疗提供了新的策略和希望。

2.1.2. 结直肠癌流行病学与病理机制

结直肠癌是全球范围内常见的恶性肿瘤之一，其发病率和死亡率总体呈现下降趋势，然而，特别值得关注的是15~49岁人群中结直肠癌的发病率(每年增加1.7%)和死亡率(每年增加0.5%)显著增加[12]。

结直肠癌的病理机制复杂,通常源于腺瘤性息肉的转化,涉及多个基因突变的累积,如 APC、TAM2、TP53 等[13] [14]。此外,错配修复缺陷和微卫星不稳定性也是结直肠癌的重要分子特征,它们与患者的预后和对治疗的反应性密切相关[15]。随着对结直肠癌病理学和分子发病机制的深入了解,未来可能开发出更多针对性的治疗方法。

2.2. 肠道菌群的多样性和功能

肠道微生物群落(肠道微生物组)是人体肠道内的微生物群落,包括细菌、真菌和病毒等[16],它们在人体内扮演着至关重要的作用,如帮助消化食物、合成维生素、调节免疫系统和维持肠道黏膜屏障。肠道微生物群落的多样性[17],即其中不同微生物种类的丰富程度和多样性水平,与人体健康密切相关。近年来的研究表明[18] [19],肠道微生物群落的多样性降低与一些疾病如肠道炎症、甲状腺疾病和糖尿病等的发生可能有关。例如, Jin Heiying 等研究者发现[20],通过一些外界或者内部作用使得肠道微生物群落多样性的降低,尤其是瘤胃球菌、念珠菌、酵母菌、肠杆菌、梭菌 IV、肠球菌、肠杆菌、乙酸弧菌等属减少的环节,其患结直肠癌的风险也随之增加。此外,肠道微生物群落的功能也备受关注,例如 Wang Mengxia 等研究者发现[21]肠道微生物-氨基酸代谢-Wnt 信号通路轴在维持肠道稳态中起着关键作用,进而对结直肠癌的抑制方面有着深刻的影响。以上研究表明肠道菌群在胃肠道肿瘤中有不同的作用,因此我们需要更深层次地了解其机制以及在临床中的应用。

3. 肠道菌群在胃肠道肿瘤中的应用

3.1. 肠道菌群在胃癌中的应用

在胃癌的治疗中,肠道菌群的作用逐渐被重视,有研究者[22] [23]尝试了多种肠道微生物的调控策略,其中益生菌法和抗生素疗法成为两种较为普遍的手段,通过摄入益生菌,能够调整肠道微生物的平衡,从而抑制肿瘤的发展和扩散。Li Junyi [24]等研究者发现乳酸菌通过引起球状转化和细胞间黏附来拮抗幽门螺杆菌,此外,还发现乳酸菌通过四种途径拮抗幽门螺杆菌,即产生抗幽门螺杆菌,抑制 *H. pylori* 定植,增强胃黏膜屏障,抗炎作用。此外,Zhang Ke 等研究者[25]发现肠道菌群的代谢产物,如短链脂肪酸中的丁酸盐通过线粒体诱导,进而抑制胃癌细胞的增殖并诱导胃癌细胞凋亡。在胃癌的诊断中,有研究者[26]发现肠道菌群也可能作为胃癌潜在的诊断标志物,已经被证实肠道菌群相关的 9 个差异表达基因可能预测胃癌患者的生存时间。此外,在胃癌的预防中,多项研究[27] [28]表明通过益生菌、益生元和菌群移植等手段调节肠道菌群,可以有效降低胃癌的发生风险,定期补充益生菌能够改善肠道菌群的结构,增加有益菌的数量,从而减少胃癌的发病机会。Liu Gan 等研究者[29]发现围手术期补充益生菌可以减少接受新辅助化疗的胃癌患者术后感染,改善短期临床结局,并降低常见炎症指标水平。以上研究者均发现肠道菌群在胃癌中的不同作用,未来我们希望通过了解更多菌群以及其在胃癌中的其他作用,以期提高胃癌患者的生存质量。

3.2. 肠道菌群在结直肠癌中的应用

在结直肠癌患者中,肠道菌群的组成与健康人群存在显著差异,表现为某些潜在的有害细菌增多,而有益菌减少[30]。例如,有研究者发现结直肠癌患者的肠道中常常能检测到较高含量的核梭菌、大肠埃希氏菌、脆弱拟杆菌等,而保护性菌属如双歧杆菌属细菌数量减少,这些菌群失调可能通过多种机制促进结直肠癌的发生,包括炎症、免疫调节、代谢活动的改变以及基因毒性物质的产生[31]-[33]。

在治疗方面,肠道菌群同样发挥着重要作用。Rong Jingjing 等研究者[34]发现口服瑞士乳杆菌 NS8 乳酸菌明显减少了肿瘤数量和增生程度,NS8 显著抑制了结直肠癌早期肠上皮细胞增殖的增加,同时提高

了细胞凋亡的水平。还有研究发现[35], 益生菌/合生元的使用可正向调节肠道微生物群, 改善术后结果、肠道屏障功能并降低结直肠癌患者的炎症参数, 因此可用作降低结直肠癌风险的干预措施。此外, Li Yangbo 等[36]研究发现通过肠道菌群发酵合成的组蛋白乙酰化抑制剂丁酸钠(NaB)有可能显著增强 5-氟尿嘧啶(5-FU)在结直肠癌治疗中的治疗效果, 并改善 CRC 患者的预后。肠道菌群也可能作为结直肠癌潜在的诊断标志物。有研究发现, 肠道微生物亚型提供了特征性肠道细菌, 如梭杆菌和拟杆菌, 通过分析肠道菌群的组成, 可以辅助结直肠癌的筛查和预后判断, 有望有助于结直肠癌的诊断[37] [38]。目前, 一些调节肠道菌群的药物也开始受到关注, 这些药物能够通过抑制有害细菌的生长, 增加有益细菌的数量, 从而达到平衡肠道菌群的目的, 为预防结直肠癌提供了新的策略[39] [40]。上述研究结果表明, 肠道菌群的调节能够影响肿瘤微环境, 增强免疫治疗的成效, 提升患者对免疫治疗的响应率, 为结直肠癌患者提供了新的治疗希望。

4. 肠道菌群与胃肠道肿瘤的潜在作用机制

4.1. 肠道菌群失衡与胃癌发生的可能相关机制

肠道微生物群的不平衡可能削弱肠道黏膜的屏障功能, 增加有害菌和毒素穿透黏膜进入体内的风险, 从而触发炎症反应, 持续的炎症状态可能损害肠道组织, 并可能加速肿瘤的形成[41]。有研究发现, 与三种胃肠道肿瘤有关的肿瘤内微生物, 如毛梭菌, 与每种肿瘤中的不同宿主途径相关, 这表明相似的微生物可以通过调节不同的宿主基因以癌症类型特异性的方式影响宿主肿瘤发生[42]。还有研究发现, 肠道菌群和人体免疫系统之间有着交互作用, 肠道菌群失衡可能导致免疫系统的异常激活或抑制, 影响机体的免疫应答, 一些致癌菌株可能通过干扰免疫系统平衡, 逃避免疫监视, 从而导致胃癌的发生[43], 因此, 肠道菌群的失衡与免疫系统的异常反应被认为是胃癌发生的重要病理途径。通过上述研究, 我们发现肠道菌群可能通过多种途径导致胃癌的发生, 故而我们还需进一步研究肠道菌群与胃癌之间的机制。

4.2. 肠道菌群代谢产物影响宿主代谢以及对胃癌的机制

肠道微生物群落对宿主的营养摄取与能量管理起着至关重要的作用, 某些代谢产物还可能通过激活致癌信号通路, 促进癌细胞增殖和转移, 因此, 肠道菌群失衡可能通过影响肠道环境来促进胃癌的发生[44]。有研究发现[45], 肠道菌群的失衡可能引发宿主代谢紊乱, 如胆汁酸和脂质代谢异常, 这些代谢紊乱与胃癌等肿瘤的形成有着密切的联系。实际上, 肠道菌群的失调不仅可能导致代谢异常, 还可能通过影响宿主的代谢状态参与胃癌的发展, 研究还表明, 特定细菌的过度生长或缺失, 以及肠道菌群的结构和多样性的变化, 都与胃癌的风险增加有关[46]。最近的研究成果进一步表明[47], 调节肠道菌群或成为胃癌治疗的新策略, 调节肠道菌群不仅能够增强化疗药物的效果, 还能减轻治疗副作用, 提升患者的生存率。这些发现为胃癌的预防和治疗提供了新的视角, 特别是在开发针对肠道菌群的新型治疗策略方面, 未来的研究可能会进一步揭示肠道菌群与胃癌之间的复杂关系, 并为胃癌的治疗提供更多的靶点。

5. 肠道菌群失衡与结直肠癌的发生机制

肠道菌群的失衡可能导致慢性炎症、代谢产物异常积累、免疫调节紊乱, 这些都是结直肠癌发病的风险因素。研究发现[48], 肠道菌群的失衡有可能会使肠黏膜受损以及发生炎症反应的概率增加, 从而导致结直肠癌发生的风险增加。还有研究发现[49], 肠道菌群失衡会导致有害菌的增殖, 这些有害菌释放的代谢产物可能对肠道黏膜细胞产生毒性作用, 损伤细胞 DNA, 从而促进癌变。失衡的菌群可能干扰肠道免疫系统的正常工作, 影响免疫细胞的分化和功能, 进而影响其对肿瘤细胞的清除能力。最新的研究指出[50], 高脂肪饮食通过在肠道炎症条件下改变肠上皮细胞代谢来驱动产生基因毒素的大肠杆菌的扩张,

进而导致结直肠癌的发生。故而，深入探究菌群失衡与结直肠癌之间的关系，不仅有助于揭示结直肠癌的发病机制，而且有望为预防和治疗结直肠癌提供创新策略。

6. 结论

综上所述，胃肠道肿瘤的发生和肠道菌群的平衡与否有着密切的关系。调节肠道菌群平衡的方法，例如通过益生菌、益生元和肠道菌群调节药物，对于预防和治疗胃肠道肿瘤产生了积极影响，具体来说，这些方法可能有助于改善肠道菌群失衡的状况，进而影响肿瘤的发生和发展。积极探索肠道菌群在胃肠道肿瘤中的角色，将有助于揭示肿瘤发生的机理，为胃肠道肿瘤的预防和治疗开拓新的途径，进一步将更好地应用于临床，从而为患者带来更好的治疗效果和生存质量。

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