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口腔菌群与消化道肿瘤关系的研究进展

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摘　要

口腔是人体内微生物菌群最丰富、最多样化的部位之一，仅次于胃肠道，由超过770种细菌组成。越来越多的证据表明，口腔内的细菌可以通过血行途径和肠道途径转移到胃肠道。口腔菌群向肠道的传播可能会加剧各种消化道肿瘤的进程。本文就口腔菌群与食管癌、胃癌、结直肠癌、胰腺癌等消化系统肿瘤关系展开综述，为后续的相关研究提供一定的参考。

关键词

口腔菌群，消化道肿瘤，研究进展

Advances in Research on the Relationship between Oral Flora and Gastrointestinal Tumours

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Abstract

The oral cavity is one of the richest and most diverse parts of the body in terms of microflora, second only to the gastrointestinal tract, and is composed of over 770 species of bacteria. There is

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growing evidence that bacteria from the oral cavity can be transferred to the gastrointestinal tract via the bloodstream and intestinal routes. The spread of oral flora to the gut may exacerbate the progression of various gastrointestinal tumours. This paper reviews the relationship between oral flora and gastrointestinal tumours such as oesophageal, gastric, colorectal and pancreatic cancers, and provides a reference for subsequent studies.

Keywords

Oral Flora, Digestive Tract Tumours, Research Advances

1. 引言

口腔是通往人体的主要门户，拥有仅次于肠道的第二大多样性的微生物群[1]，口腔内的各种微生物栖息地(如牙齿、颊黏膜、软腭和硬腭、舌头)使生态系统变得极其复杂，并吸引了多种微生物，包括细菌、真菌、古菌、病毒等，其中细菌是主要成分。近年来，随着高通量测序、宏基因组学、基因芯片等分子生物学技术的发展，人们对各种疾病中微生物的分布有了清晰的认识，口腔微生物菌群的相互作用能够保护人体避免受到外界不良刺激的侵犯，当口腔微生物菌群失衡时，将会导致各种系统性疾病的发生，如心血管疾病、不良妊娠结局和类风湿关节炎、消化道肿瘤等，牙周微生物从口腔栖息地传播到远处部位，并破坏其免疫监测和稳态，以促进或加速致病过程。此外，牙龈炎尤其被认为是类风湿关节炎自身抗体产生的潜在原因[2] [3] [4]。此外，研究证实[5]在结肠癌患者的肠腔内和肠道黏膜组织中发现了典型口腔细菌的异常富集，口腔菌群与胃肠道肿瘤密切相关，其致癌机制可能包括致癌物质的产生、慢性炎症和细胞代谢的改变等[6]。

2. 口腔菌群与食管癌

食管癌是我国常见的一种高发病率和高死亡率的消化道恶性肿瘤，根据组织病理的不同，主要分为食管鳞状细胞癌和食管腺癌。Machiko [7]研究发现食管癌患者口腔微生物菌群与健康者相比呈现出显著差异，食管癌患者较健康者相比放线菌和心绞痛链球菌的丰度显著提高。此外 Narikiyo 等人[8]发现唾液中牙密螺旋体、脓毒性链球菌和心绞痛链球菌可能通过刺激中性粒细胞和单核细胞的招募和激活在食管癌的进展中发挥重要作用。Brandilyn 等人[9]的一项前瞻性队列研究中，发现口腔中牙周病原体连翘单核菌与食管腺癌风险增加有关，奈瑟菌和肺炎链球菌的缺失与食管腺癌风险降低有关，并且口腔中牙龈卟啉单胞菌的丰度增加有提高食管鳞癌发病风险的趋势。同时，这也在另一项研究中得到了证明[10]。

关于微生物群变化是如何引起食管癌发生发展的，机制尚不明确，Brooke [11]在通过 16S rRNA 基因测序对食管微生物检测中发现，在健康人群中革兰氏阳性菌占主导地位，而革兰氏阴性菌在包括反流性食管炎和进 Barret 食管中占主导优势。在牙周组织中，IL-1β 主要来源于巨噬细胞、中性粒细胞、成纤维细胞和肥大细胞。这些细胞在被革兰氏阴性细菌细胞壁的主要成分脂多糖激活后合成 IL-1β，IL-1β 诱导破骨细胞形成和骨吸收，进而导致牙周组织的局部炎症变化。

此外，该细胞因子刺激磷脂酶 A2、前列腺素、急性期合成蛋白、IL-6、肿瘤坏死因子和许多基质金属蛋白酶(MMPs)的释放[12]，IL-1β 还能够激活内皮细胞的 NF-κB 信号通路，从而促进血管内皮生长因

子(VEGF)等促血管生成因子的表达和分泌。这些促血管生成因子可以刺激内皮细胞增殖、迁移和不同化，进而形成新的血管网络，提供肿瘤细胞所需的营养和氧气，IL-1β 也可以诱导其他炎症因子的产生，如肿瘤坏死因子(TNF-α)、IL-6 等，这些因子也可以促进肿瘤生长和进展。IL-1β 在肿瘤进展中扮演着重要的促进作用，同时也是肿瘤炎症微环境的重要组成部分[13]。IL-1β 的高含量与肿瘤的侵袭性、迁移和侵袭性更强的肿瘤表型相关[14] [15]。在 Wang 等人的研究中，IL-1β 的低表达会导致 E-cadherin 的低表达，进而促进细胞迁移[16]。Li 采用实时荧光定量聚合酶链反应和免疫组化方法对食管癌组织进行分析发现，E-cadherin 在有转移的食管癌中表达明显低于无转移的食管癌及边缘组织，E-cadherin 的低表达与细胞功能紊乱、凋亡、生长抑制、细胞周期阻滞相关，使肿瘤侵袭性增强，患者生存期降低[17] [18]。同时，IL-1β 诱导 MMP-9，MMP-9 在局部细胞外基质降解和肿瘤侵袭中发挥作用。E-cadherin 介导的黏附缺失和 MMP-9 导致的细胞迁移增加增加是肿瘤从良性转变为侵袭性转变的重要标志。

另一个重要的促炎细胞因子是 IL-6。它是牙周组织的许多细胞在脂多糖和促炎细胞因子 IL-1β 和 TNF 的刺激作用下产生的。IL-6 诱导骨吸收，刺激急性期合成蛋白、趋化因子和 PGE2 [19] [20]。IL-6 还可诱导氧化应激，并可导致线粒体中过氧化物的短暂积累，从而导致线粒体损伤[21] [22]。IL-6 还通过增加 MMPs 表达来影响细胞的侵袭和转移过程[23]。此外，该细胞因子上调各种粘附分子和内皮白细胞粘附分子的表达，使肿瘤细胞与内皮细胞粘附，从而影响肿瘤扩散[24]。大多数 IL-6 的靶向基因参与细胞周期进展和凋亡抑制。通过影响抗凋亡通路，IL-6 可能影响癌症的发展。

3. 口腔菌群与结直肠癌

结直肠癌是一种常见的恶性肿瘤，死亡率高，仅次于肺癌世界癌症死亡的第二大原因。近年来，微生物对结直肠癌的贡献越来越突出，累积的证据表明，微生物失调在结直肠癌的发生中起着相当重要的作用[25]。一项大型队列研究[26]调查了结直肠癌与口腔微生物菌群相关的相关性，通过基因测序对唾液样本进行分析，结果表明口腔菌群中如双歧杆菌科和普雷沃菌与结直肠癌发病风险增加正相关，而肉芽胞杆菌科、丹毒杆菌科、普雷沃菌科、链球菌与结直肠癌发病风险降低相关。Flemer 和 Zhang [27] [28] 通过比较结直肠癌患者和健康对照组的唾液样本，发现其口腔菌群特征存在显著差异，结直肠癌患者口腔菌群中与结直肠癌相关的口腔病原菌的丰度显著增加，如梭杆菌、普雷沃菌、卟啉单胞菌。Kostic [29] 在研究中表明了在结直肠癌发生过程中，核酸杆菌从正常组织到腺瘤组织再到腺癌组织的丰度逐渐增加，Komiya [30]等人证实，在结直肠癌患者的唾液和结肠肿瘤中都检测到相同的核酸杆菌，表明结肠癌中定植的核酸杆菌起源于口腔微生物菌群。

而与其他细菌不同的是，核酸杆菌对结直肠癌的发病机制的影响已得到深入的探讨。蛋白 Fap2 和 FadA 在结直肠癌研究中越来越受到关注。Fap2 作为核酸杆菌的上一种半乳糖敏感的血凝素和粘连素，可能在核酸杆菌的侵袭潜能中发挥重要作用[31]。Fap2 蛋白通过直接激活抑制 T 细胞和 NK 细胞受体，抑制 T 细胞和 NK 细胞的杀伤肿瘤活性，从而产生肿瘤免疫逃逸机制[32]，此外，核酸杆菌诱导的肿瘤微环境改变通过招募肿瘤浸润的骨髓来源的抑制细胞(MDSC)促进结直肠癌的进展[33]。Fap2 结合碳水化合物部分 D-半乳糖-β(1-3)-D-乙酰-D-半乳糖胺(GalGalNAc)，在结直肠癌中高表达，并通过血行途径促进核酸杆菌与结直肠癌细胞的结合[34]。Fap2 还诱导促炎细胞因子 IL-8 和 C-XC 基序趋化因子配体 1 (CXCL1)的分泌，加速结直肠癌细胞迁移[35]。另一种核酸杆菌粘附蛋白 FadA 通过激活 E-cadherin/β-catenin 信号通路促进结直肠癌的发生，从而刺激 CRC 细胞增殖[36]。同时也发现 FadA 通过激活 Wnt/β-catenin 调节因子 Annexin A1 促进结直肠癌[37]。此外，核酸杆菌通过刺激 TLR4/MYD88/NF-κB，增强细胞自噬抑制剂(miR-21)的表达，进而抑制 RASA1 的表达并激活 MAPK 通路，促进结直肠癌细胞增殖[38]。这些研究表明，核酸杆菌通过定位、增殖、免疫抑制、转移和化疗耐药等途径促进结直肠癌的发生发展。

4. 口腔菌群与胰腺癌

胰腺癌是一种恶性程度极高的肿瘤，来源于胰腺腺泡和导管细胞，其中胰腺导管腺癌是胰腺癌中最常见的类型。Fan [39]等人的研究显示，口腔微生物菌群中牙龈卟啉单胞菌和放线菌聚集菌与胰腺癌发病风险升高相关。而纤毛菌属及梭杆菌门与胰腺癌发病风险降低相关。Michaud [40]分析了口腔微生物菌群的相关抗体与胰腺癌之间的关系，发现牙龈卟啉单胞菌 ATTC 53978 (一种致病性牙周细菌)抗体水平高的个体胰腺癌发病风险较抗体水平低的个体高约 2 倍以上。Vogtmann [41]等人将胰腺癌患者及其匹配对照组的口腔微生物群进行了分类。他们发现肠杆菌科、拟杆菌科和葡萄球菌科在胰腺癌患者中增加，而嗜血杆菌在对照组中增加。为了探索胰腺癌患者的口腔微生物特征，Torres [42]等人分析了胰腺癌患者和健康对照者唾液中的口腔微生物群组成。发现胰腺癌患者中纤毛菌与牙龈卟啉单胞菌的比例显著提高。

胰腺炎症的一个原因是口腔、胃或肠道微生物群的失调，这可能导致有害细菌的过度生长。这可能导致上皮屏障破裂，细菌迁移到胰腺。胰腺持续的细菌定植导致持续的炎症，并促进癌症的发展。微生物产物或代谢物通过维持炎症和免疫调节支持肿瘤生长。细菌产物如脂多糖、短链脂肪酸、脂蛋白、脂肽和单链或双链 DNA，可通过结合模式识别受体(PPR)和激活 toll 样受体(TLR)诱导免疫抑制。这通过免疫逃避促进肿瘤生长，特别是在早期癌变过程中[43]。炎症也可以通过其致癌作用促进胰腺癌的发展。胰腺组织的慢性炎症可在胰岛素阳性内分泌细胞中引发 KRAS 致癌突变，诱导上皮细胞分化，导致胰腺癌[44]。几乎所有的胰管腺癌都有 KRAS 基因突变[45]，尽管 KRAS 是一种常见的突变，但 KRAS 的激活仍然需要脂多糖驱动的炎症的过度刺激[46]。活化的 KRAS 可通过 NF-κB 通路进一步推进癌症的发生[47]。

牙龈卟啉单胞菌能够激活多种抗凋亡/促生存途径，并通过部分阻断线粒体依赖的凋亡来维持宿主细胞的生存。这些激活途径包括 JAK/PI3K/Akt 和 JAK/STAT3，最终导致抗凋亡基因 Bcl-2、Bcl-xL 上调，抗凋亡 Bcl-2 和 Bcl-xL 蛋白能够抑制细胞色素 C 的释放，从而最终抑制细胞色素 C 激活凋亡级联反应，促进癌症细胞存活和增殖[48]。Ikezawa [49]等人表明，90%的胰腺癌存在 Bcl-xL 过表达。此外，牙龈卟啉单胞菌分泌的半胱氨酸蛋白酶刺激蛋白酶活化受体，进而激活 NF-κB 通路。同时，牙龈卟啉单胞菌入侵宿主细胞后可激活 erk1/2-Ets1 和 p38/HSP27 通路。以上 3 种途径共同诱导基质金属蛋白酶原(proMMP-9)的表达，活化的(MMP-9)通过降解各种细胞外基质，可能在肿瘤侵袭和转移中发挥重要作用[50]。

5. 口腔菌群与胃癌

胃癌是常见的消化系统恶性肿瘤，也是全世界癌症死亡的第五大原因。幽门螺杆菌引起粘膜炎症和胃的盐酸分泌腺的进行性破坏，造成微生物在胃中定植，在癌变级联的初始阶段起着至关重要的作用，并且相关研究表明[50]幽门螺杆菌感染后其他细菌的存在促进胃癌的发展。Wu [51]等人的研究证明胃癌患者与健康对照组的口腔菌群总体组成存在显著差异，并且在属水平上，链球菌与胃癌的发生风险成正相关，而奈瑟菌属、普雷沃菌属和卟啉单胞菌属与胃癌的发生风险成负相关。

幽门螺杆菌被认为是胃癌的重要致病因子。幽门螺杆菌可分为细菌癌蛋白细胞毒素相关基因 A (CagA)阳性菌株和 CagA 阴性菌株。在一项 meta [52]分析中 CagA 阳性株感染患者胃癌的风险较高，这与此前报道的 CagA 抗体阳性患者肿瘤风险较高相一致[53]。幽门螺杆菌能够将整合素 CagA 注入宿主胃上皮细胞中，CagA 经过酪氨酸磷酸化后，能够激活多个信号通路。磷酸化的 CagA 通过与活化的 SHP2 相互作用形成 CagA-SHP2 复合物。CagA-SHP2 [54]通过 Ras 依赖和 Ras 不依赖的方式增强 Erk-MAP 激酶信号传导的强度，从而增加细胞迁移能力[55]。此外，非磷酸化的 CagA 会损害细胞内信号网络，非磷酸化的细胞内 CagA 与 E-cadherin 相互作用，破坏 E-cadherin-β-catenin 复合物，导致核 β-catenin 的积累，参与癌变相关的靶基因的转录 CagA [56]。同时可激活 STAT3 通路，激活的 STAT3 通路受宿主免疫反应驱动，

与幽门螺杆菌诱导的胃炎和癌症进展相关，与 CagA 磷酸化无关[57]。Cag 分泌系统还通过外膜囊将幽门螺杆菌肽聚糖输送到宿主细胞，肽聚糖随后激活 PI3K-AKT，调节细胞迁移、增殖和凋亡[58]。除 Cag 外，空泡毒素 A (VacA)是幽门螺杆菌的另一个主要毒力决定因素 Nakayama 等人报道 VacA 通过 PI3K 依赖方式激活 β-catenin [59]。炎症和癌症之间的因果关系已得到充分认识。幽门螺杆菌利用毒力因子 CagA、VacA 和肽聚糖上调促炎因子 IL-1、IL-6、IL-8、TNF-α 和 NF-κB，激活 NF-κB 信号在胃上皮细胞和循环免疫细胞中的级联反应，细胞因子的产生触发白细胞的激活和迁移，以及细胞因子、趋化因子和粘附因子的级联调控，共同参与胃癌的形成[60]。

6. 小结与展望

近年来随着测序技术的发展，口腔菌群与消化道肿瘤之间的联系被慢慢揭开，例如幽门螺杆菌与胃癌、核酸杆菌与直肠癌的密切关系等，口腔菌群有成为筛查消化道肿瘤的工具潜在可能。多项研究证明，口腔菌群可以通过诱导慢性炎症、影响细胞的代谢以及产生致癌物质等多种方式参与消化道肿瘤的发生发展，但具体机制，现在仍不清楚，需要更多更加深入的研究来阐明其复杂机制，为我们对消化道肿瘤的预防、诊断、治疗及预后提供有力的帮助。

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