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Review 综述

“口-肠轴”视域下：消化链球菌在结直肠癌演进中的作用

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摘　要：结直肠癌(colorectal cancer, CRC)是全球高发的消化道恶性肿瘤，其病理进程不仅与肠道微生态失衡高度相关，越来越多的研究提示口腔微生态也在其中扮演着重要角色。新兴的“口-肠轴”理论为阐释微生物的跨器官调控提供了新视角。近期研究表明，消化链球菌属(*Peptostreptococcus*)作为口腔微生物群落的主要成员，其异常变化与 CRC 的发生发展在时间和空间维度上均存在关联，可能通过“口-肠轴”途径调控肠道微生态及 CRC 病理演进。本文回顾了口腔与肠道的微生态对话，分析了消化链球菌[如胃消化链球菌(*P. stomatis*)、厌氧消化链球菌(*P. anaerobius*)]与 CRC 之间的多维关联，包括其在不同临床特征的 CRC 患者中呈现的群体异质性，以及其在“腺瘤-癌”病理阶段的动态演变规律和空间分布特征。总结了消化链球菌通过促进肿瘤细胞增殖、诱导上皮-间充质转化、重塑肿瘤微环境等方式影响 CRC 病程的作用机制。此外，本文还进一步探讨了消化链球菌作为 CRC 预测标志物及治疗靶点的临床应用潜力，提出未来可开发针对口腔源性微生物的干预策略，以期激发研究者对该领域的研究兴趣并推动深入研究。

关键词：口-肠轴；结直肠癌；消化链球菌；作用机制；生物标志物

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From the perspective of the “oral-gut axis”: the role of *Peptostreptococcus* in colorectal cancer progression

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Abstract: Colorectal cancer (CRC), a common malignant neoplasm of the digestive system globally, demonstrates pathological progression that is intricately linked not only to dysbiosis of the gut microbiota but also to the oral microbial ecosystem. The emerging concept of the “oral-gut axis” offers novel insights into the regulation of microbial interactions across different organs. Recent research indicates that *Peptostreptococcus*, a predominant genus within the oral microbiome, exhibits spatiotemporal correlations with the initiation and progression of CRC. This genus may influence intestinal microecological changes and CRC pathogenesis through the “oral-gut axis”. We explore the microbial interactions between oral and intestinal ecosystems, examining the multidimensional associations between specific *Peptostreptococcus* species (such as *P. stomatis* and *P. anaerobius*) and CRC development. Key considerations include the population heterogeneity of these species among CRC patients with varying clinical profiles, their dynamic evolution during the adenoma-carcinoma sequence, and their spatial distribution across different pathological stages. We synthesize mechanistic evidence illustrating the role of *Peptostreptococcus* in promoting tumorigenesis by enhancing cancer cell proliferation, inducing epithelial-mesenchymal transition, and remodeling the tumor microenvironment. Additionally, this article assesses the clinical potential of *Peptostreptococcus* as predictive biomarkers and therapeutic targets for CRC. Finally, we propose future directions for the development of targeted microbial intervention strategies against oral-derived pathogens, with the aim of stimulating scientific interest and encouraging further investigation in this emerging research area.

Keywords: oral-gut axis; colorectal cancer; *Peptostreptococcus*; mechanism of action; biomarker

“口-肠轴”是人类健康领域的一个新兴关键维度。随着 21 世纪新一代测序技术的进步，研究者突破了传统静态单部位微生物研究的局限，开始系统性地探索跨器官微生物关联。在此背景下，“口-肠轴”理论体系逐步形成。2017 年，Acharya 等[1]基于口腔微生物及其代谢物、炎症因子可能穿过受损肠道屏障的假设，对“口-肠轴”进行了初步探究。2018 年，Du Teil Espina 等[2]正式确立了口腔-肠道微生物组轴概念。2021 年，Park 等[3]首次揭示了“口腔-肠道微生物轴”在胃肠道疾病和癌症中的双向调控机制，创新性提出口腔致病菌可通过破坏肠黏膜屏障和重塑肿瘤微环境促进结直肠癌(colorectal cancer, CRC)的发展。

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CRC 已成为世界范围内发病率居第三、死亡率居第二的恶性消化系统肿瘤[4-5]。其发生发展受遗传、环境等多重因素的复杂交互影响，其中微生物发挥了重要作用。据报道，在健康和疾病人群中消化链球菌属(*Peptostreptococcus*)、链球菌属(*Streptococcus*)、放线菌属(*Actinomyces*)等常见口腔微生物是沿胃肠道的广泛传播者[6]，而具核梭杆菌(*Fusobacterium nucleatum*)作为偶然传播者已有充分证据表明其可通过促进肿瘤免疫逃逸、化疗耐药等机制参与 CRC 的演进[7-8]。最近研究发现，另一机会致病菌——消化链球菌属也可选择性富集于 CRC 患者的粪便和黏膜微生物群中[9]。消化链球菌属是一组革兰氏阳性厌氧菌，常与梭杆菌属(*Fusobacterium*)、卟啉单胞菌属(*Porphyromonas*)共聚集并定居于口腔[10]。此外，它还存在于上呼吸道、肠道和女性生殖道[9]。尽管有可靠的证据表明消化链球菌属可能参与 CRC 的发生发展，但该菌属与肠道微生态的相互作用及其参与肿瘤进展的机制尚未得到有效整合。因此，本文在“口-肠轴”视域下总结消化链球菌属与 CRC 的最新研究进展，分析该菌属通过“口-肠轴”影响 CRC 的可能途径，概述其在不同临床特征的 CRC 患者群体中的异质性、“腺瘤-癌”序列演变中的动态规律、空间分布特征及其在不同分子亚型中的分布差异，阐明其致癌机制，并探讨其在 CRC 临床诊断和治疗等方面的应用前景及挑战(图 1)。希望本文能够促进研究者对“口-肠轴”的深入认知，为开发基于微生物组调控的消化道疾病干预策略提供全新视角。

1 口腔与肠道的微生态对话

口腔与肠道作为消化道的两端，不仅在解剖上连续，且同属黏膜免疫系统，还通过中枢神经系统进行信号交流[11]。从微生态学角度看，二者是人体中 2 个最大的微生物栖息地[12]。随着多组学技术的发展，这 2 个生态位点的微生物群落组成、代谢活动、环境因子及其相互作用规律不断被拓展。肠道微生态以其庞大的生物多样性著称，目前已鉴定出 1 000 余种微生物，主要由拟杆菌门(*Bacteroidota*)、芽孢杆菌门(*Bacillota*)和放线菌门(*Actinomycetota*)的厌氧菌组成[13]。在由黏液层、肠上皮和适宜 pH 值等构成的独特肠道环境内，这些微生物及其短链脂肪酸等代谢物与宿主相互作用，共同参与消化代谢、免疫调节及神经刺激等关键生理过程[14-15]。口腔作为仅次于肠道的第二大微生态系统，包含 770 多种细菌，涵盖放线菌门、拟杆菌门、芽孢杆菌门等 7 个主要门类，主要以生物膜形式聚集在口腔黏膜、唾液、牙龈斑块等位置；这种特殊的定殖模式与环境中的唾液流、氧气梯度等因素共同塑造了口腔微生态的结构与功能，从而维持口腔微生态平衡[16-17]。

一般情况下，口腔和肠道的微生态系统并不共享，仅有极少部分微生物分类群相同。然而，当口肠屏障功能发生障碍时这 2 个生态位之间可能形成病理性信号交流。具体而言，一方面肠道微生态失衡可能通过免疫调节等途径引起全身炎症反应，破坏口腔黏膜屏障的免疫功能，或通过粪-口传播途径从而引发口腔微生态失调并促进牙周炎等口腔疾病发生[18-19]；另一方面，口腔中的微生物，例如 *F. nucleatum*、牙龈卟啉单胞菌(*Porphyromonas gingivalis*)及其毒性代谢物也可突破屏障限制而移位定殖于肠道，进一步改变肠道微生态[20-21]。上述 2 种模式建立了“口腔-肠道微生物组轴”的病理联系，其发生机制可能涉及两大核心要素：一是不同生态位固有的生理差异被破坏，包括 pH 梯度、氧分压、营养供给等环境参数异常改变；二是机体出现菌群失调、局部炎症反应及免疫功能受损等病理改变而诱导的口腔-肠道屏障功能受损[12,22]。相比之下，这种异常的“口-肠轴”变化在消化道疾病发生发展中发挥重要作用，尤其与溃疡性结肠炎、CRC 等肠道疾病的病理进展紧密相连[3,12]。

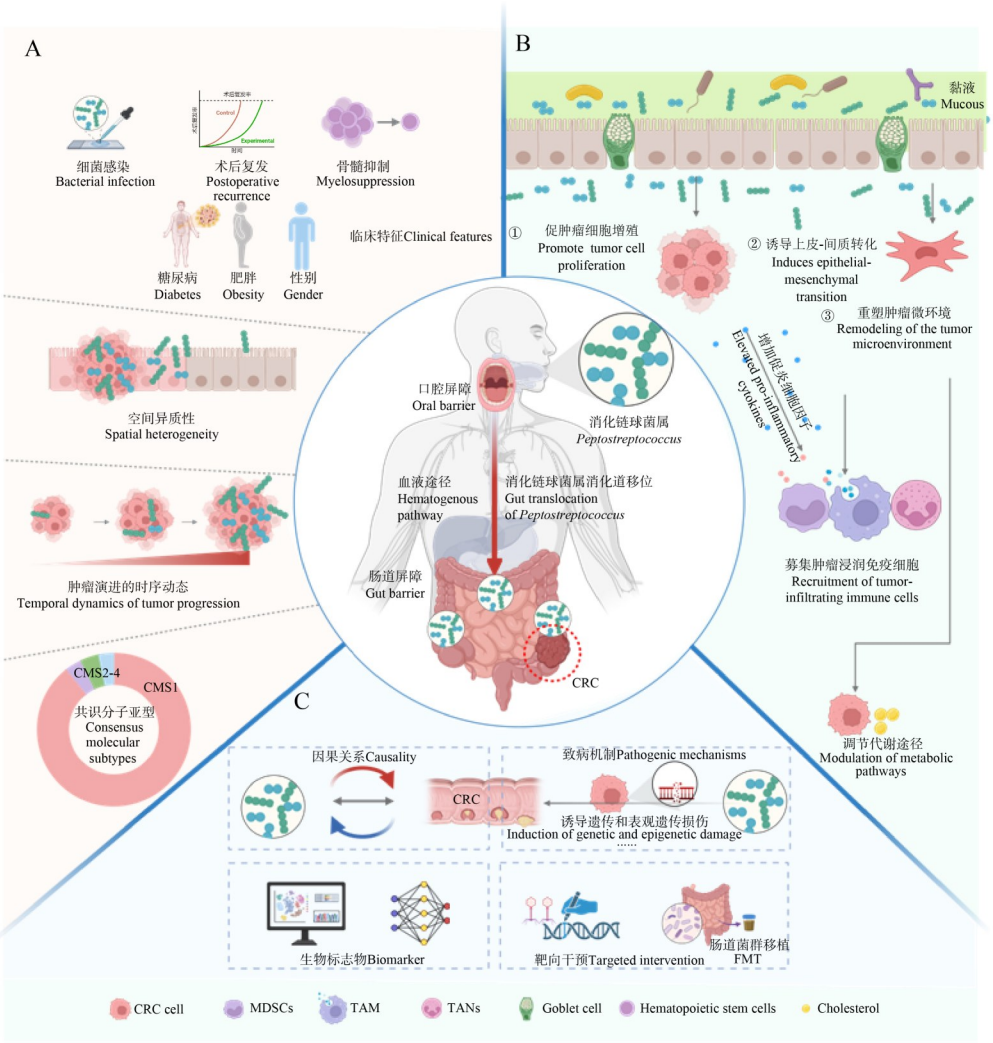

图1 “口-肠轴”视域下消化链球菌与CRC。A：消化链球菌属的分布特征(其丰度分布与患者体重指数、性别、肿瘤术后复发、化疗后骨髓抑制等临床特征，以及CRC不同空间位置、“腺瘤-癌”进展的不同阶段和不同分子亚型密切相关)；B：消化链球菌属致癌机制，包括促进肿瘤细胞增殖、诱导上皮-间充质转化、重塑肿瘤微环境(募集肿瘤浸润免疫细胞、增加促炎细胞因子释放、调节代谢途径)；C：展望(探究消化链球菌属在CRC中的因果关系、致癌机制，及其作为生物标志物及治疗靶点的潜力)。

Figure 1 Role of *Peptostreptococcus* in CRC under the “oral-gut axis” perspective. A: Distribution characteristics of *Peptostreptococcus* (Its distribution is linked to clinical factors like body mass index, gender, tumor recurrence, and chemotherapy-induced myelosuppression, as well as CRC’s spatial locations, progression stages, and molecular subtypes); B: *Peptostreptococcus* promotes CRC by enhancing tumor cell proliferation, inducing epithelial-mesenchymal transition and reshaping the tumor microenvironment, such as recruiting tumor-infiltrating immune cells, increasing proinflammatory cytokines, and regulating metabolic pathways; C: Perspectives (Research is needed to explore *Peptostreptococcus*’ role in CRC, its carcinogenic mechanisms, and potential as biomarkers and treatment targets). FMT: Fecal microbiota transplantation; TAM: Tumor-associated macrophage; TANs: Tumor-associated neutrophils.

近年来，CRC 的微生物组学研究已取得显著进展。虽然肠道固有菌群在该疾病中的作用已被广泛阐明，但越来越多的证据表明“口-肠轴”的病理性变化，特别是口腔来源微生物如 *F. nucleatum*、*P. gingivalis* 的肠道异位定殖及其毒力因子的异常扩散在 CRC 发生发展中同样扮演关键角色，它们可通过促肿瘤细胞增殖、介导免疫逃逸等机制参与 CRC 进程[7-8]。前期研究也通过模拟口腔源性 *F. nucleatum* 的肠道定殖，证实了其可借助表面黏附素与肠上皮 E-钙黏蛋白结合，激活下游信号通路，促进炎症微环境向肿瘤微环境转化，且中药复方干预进一步验证了该调控通路的可靶向性[23-24]。值得注意的是，最新研究发现消化链球菌属同上述常见口腔优势菌共同存在于与 CRC 相关的黏膜微生物群中[9]。消化链球菌属作为革兰氏阳性厌氧菌，菌体呈圆形或卵圆形，最早由 Kluyver 和 Van Niel 于 1936 年分离鉴定；该属中常见菌种包括厌氧消化链球菌(*P. anaerobius*)、胃消化链球菌(*P. stomatis*)、罗素氏消化链球菌(*P. russellii*)等[25-27]，其中前两者属于口腔常驻成员。作为机会致病菌，多项研究证实该菌属可通过异常增殖促进牙周病、炎症性肠病、胃癌，特别是 CRC 的发生发展[28-30]，这也为揭示口腔-肠道的微生态对话提供了新的研究方向。

2 口腔源性消化链球菌与 CRC 的关联

据美国国立卫生研究院“人类微生物组计划”数据库显示，消化链球菌属在健康个体口腔样本的相对丰度高于粪便样本[31]。另一项研究对 807 例 CRC 患者的肿瘤组织进行全转录组测序，并与已发表的 CRC 患者唾液和粪便微生物组数据对比，同样发现该菌属在口腔中的存在更普遍[32]，提示其可能源于口-肠的“被动”微生物传播。Schmidt 等[6]发现无论是健康个体还是 CRC 患者，*P. stomatis* 都是其口-粪传播途径的主要成员，且代表口腔微生物渗入肠道的“口腔-肠道评分”在 CRC 中也显著升高[6,33]，而已被证实 CRC 肠道与口腔具有相同菌株的 *F. nucleatum* 却是偶然传播者[34]。此外，Flemer 等[35]分析显示 CRC 患者口腔和结肠组织具有相似的细菌丰度网络，消化链球菌属是其中一员，并常与 *F. nucleatum*、*P. gingivalis* 等口腔菌共同被检测出[10,36]，进一步验证其口腔源性定殖倾向。目前 *F. nucleatum*、*P. gingivalis* 等口腔微生物通过“口-肠轴”的传播方式主要包括经消化道传播和经血液传播等[37-38]，而消化链球菌属也具有类似的作用路径。对经抗生素处理的 $APC^{min/+}$小鼠灌胃给予 *P. stomatis*/*P. anaerobius*，CRC 组织共定位结果验证了其可通过肠内途径向肠黏膜定殖[39-40]。进一步研究证实，该菌属可降低紧密连接蛋白表达而损害肠道屏障功能[39]，为其肠内移位提供了理论依据。作为牙周致病菌[41]，该菌属也可能在牙龈溃烂时经血液迁移至肠道致病，且临床研究指出其可引发菌血症并增加 CRC 风险[42]，这一血液途径尚需进一步验证。当消化链球菌属移位至肠道后可借助其表面蛋白如果糖-1, 6-二磷酸醛缩酶(fructose 1, 6-bisphosphate aldolase, FBA)黏附定殖于肠黏膜，并刺激 CRC 细胞恶性增殖[39]。这与 *F. nucleatum* 利用黏附素定殖肠黏膜的机制类似[43-44]，提示这可能是口腔微生物移位定殖的通用机制。综上所述，消化链球菌属可能通过肠内或血液途径实现口腔-肠道的跨器官传播，并通过其表面黏附蛋白定殖于肠黏膜进一步引发 CRC (图 1)。越来越多的证据表明，该菌属及其代谢物在肠道的富集与 CRC 存在普遍关联[39,45-51]。

2.1 消化链球菌在 CRC 患者中的群体异质性

消化链球菌属的丰度与特定 CRC 群体呈显著正相关(图 2A)。研究指出，该菌属在肿瘤组织中的存在不仅与 CRC 患者较短总生存期相

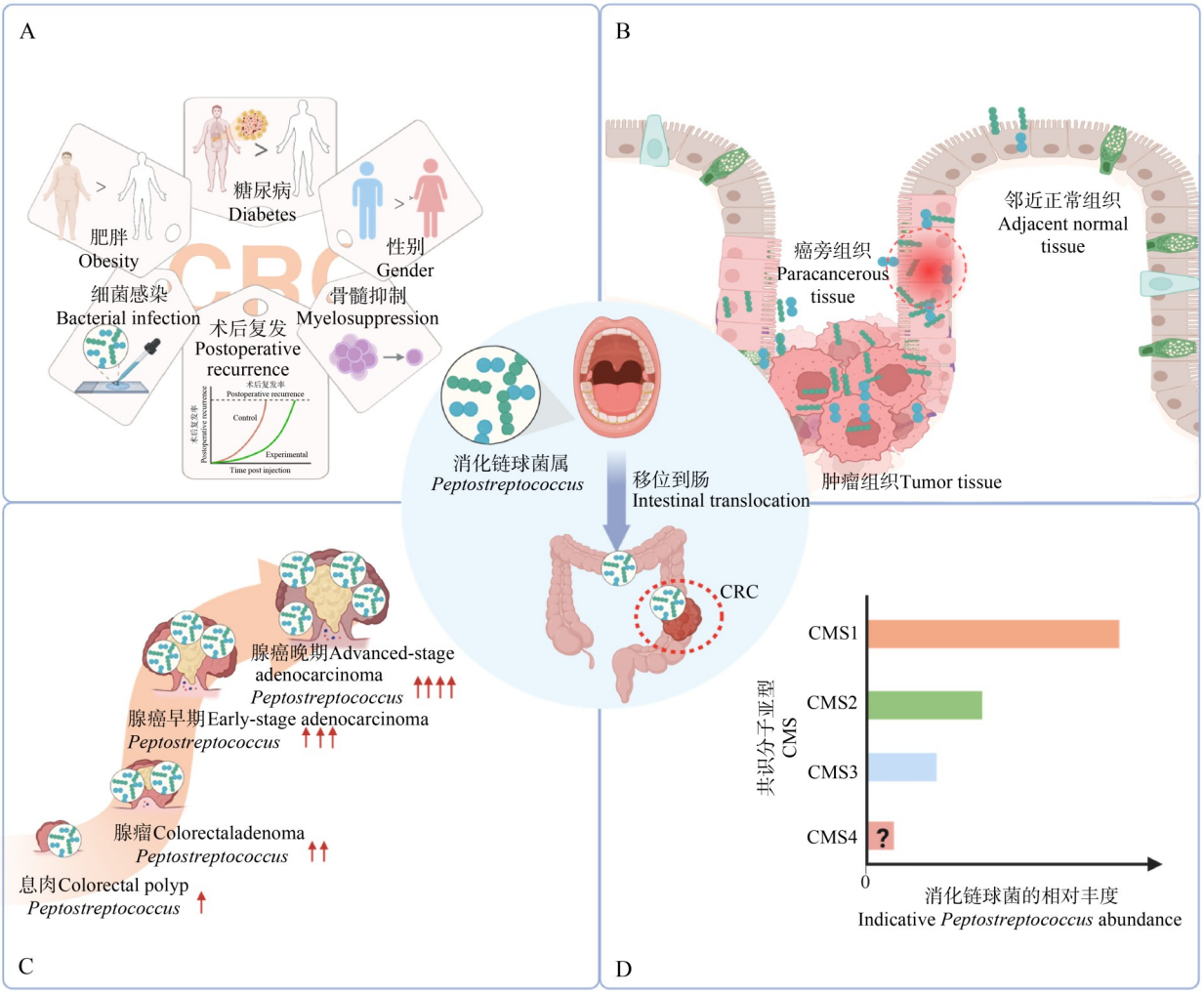

图2　口腔源性消化链球菌与CRC的关联。A：消化链球菌属在CRC不同临床特征中的差异；B：消化链球菌属在CRC不同空间位置的分布；C：消化链球菌属在CRC “腺瘤-癌”进展过程中的变化；D：消化链球菌属在不同分子亚型CRC中的差异。条形长度代表消化链球菌在CMS亚型中的示意性相对丰度，反映趋势为CMS1>CMS2>CMS3 (无定量数据)。

Figure 2　The association between oral-origin *Peptostreptococcus* and CRC. A: Differences in *Peptostreptococcus* abundance across clinical features of CRC; B: Spatial distribution of *Peptostreptococcus* in CRC; C: Dynamics of *Peptostreptococcus* in the adenoma-carcinoma sequence of CRC; D: Differences in *Peptostreptococcus* abundance across molecular subtypes of CRC. The bar length indicates schematic relative abundance of *Peptostreptococcus* across CMS subtypes, reflecting the trend CMS1>CMS2>CMS3 (no quantitative data available).

关[52]，还可增加术后复发风险[53]及化疗后骨髓抑制发生率[54]，提示其可作为 CRC 的不良预后标志物。*P. stomatis* 的丰度还可随体重指数同步增长，且在肥胖状态下其可与益生菌普氏栖粪杆菌(*Faecalibacterium prausnitzii*)发生交叉喂养，进而协同促癌[55]。同时该菌属在糖尿病合并

CRC 患者中异常富集[56]，提示其在代谢相关 CRC 中的介导作用。此外，Kwong 等[42]通过一项大型队列研究表明，该菌属引发的菌血症患者发生 CRC 风险更高。Yu 等[57]通过第三代 Pacific Biosciences (PacBio) 测序发现 *P. anaerobius* 是雄性 CRC 的显著特征菌。尽管有研究指出其丰度未显示显著年龄[58]或地域差异[59]，但该菌属在 CRC 的群体特异性已得到充分证据支持，为高危人群的早筛、早诊提供潜在靶点。

2.2 消化链球菌在 CRC 病理进程中的空间定殖特征

消化链球菌属在 CRC 的分布表现出显著的空间异质性(图 2B)。Zhang 等[60]通过分析 CRC 患者不同结肠组织(正常、癌旁、癌性)内细菌的富集属，发现 *P. anaerobius* 在肿瘤组织中含量更丰富。体外实验证明[40]，该菌在 CRC 细胞系的附着率显著高于正常结肠黏膜上皮细胞系。最近一项研究比较分析了 CRC 和结肠息肉患者组织样本中共有的 17 个操作分类单元，并基于其在肿瘤样本中的丰度进行聚类，发现与远端肿瘤组织相比 *P. stomatis* 在近端肿瘤黏膜中更丰富[35]。进一步研究表明，消化链球菌属可扩散到邻近正常组织，且其丰度从肿瘤组织近端到远端呈逐渐递减趋势[61]。此外，该菌属的丰度在不同样本类型间也存在差异，如结肠黏膜样本高于粪便样本[62]，总的来说，消化链球菌属在 CRC 的分布存在空间异质性，即以近端肿瘤黏膜区域为富集核心，并随着向正常组织过渡而逐渐降低，而该黏膜特异性分布模式能够便于其与肠上皮细胞互作，进而增强与 CRC 的关联。

2.3 消化链球菌在 CRC 发生发展中的时序演变规律

消化链球菌属的动态变化与 CRC 进展密切相关(图 2C)。Hua 等[63]发现消化链球菌属是结直肠“腺瘤-癌”相关细菌网络中的关键属，可以作为诊断和治疗 CRC 及癌前病变的潜在标志物。多项研究证实，在结直肠“腺瘤-癌”演变中消化链球菌属的水平随着疾病进展而显著增加[47,64-65]。此外，在 CRC 后期进程中该菌属也呈现出相同的增长趋势[66-67]。研究表明 *P. anaerobius* 在 CRC 患者中的阳性检出率高于健康人群，且富集于晚期 CRC[68]。Ge 等[69]发现与低危 CRC 相比，高危 III 期 CRC 中富含消化链球菌属，提示该菌属在促 CRC 进展中扮演重要角色，可作为病程演进的预测分子。

2.4 消化链球菌在不同分子亚型 CRC 中的分布特征

CRC 共识分子亚型(consensus molecular subtypes, CMSs)是基于基因表达等分子特征划分的 4 个亚型(CMS1–CMS4)，各亚型具有独特的生物学特性，预后及治疗反应也存在差异。研究表明可通过肿瘤特异性微生物对 CRC 的分子亚型进行鉴别分析[70]。Purcell 等[36]基于转录组与宏基因组测序发现，与其他分子亚型相比 *P. stomatis*、*F. nucleatum* 和 *P. gingivalis* 在 CMS1 中高度富集(图 2D)。CMS1 亚型被描述为免疫原性亚型，其特点是免疫反应激活和微卫星不稳定性(microsatellite instability, MSI)[71]。通过对 275 名 CRC 患者和 95 名健康人的粪便样本进行 16S rRNA 基因测序发现，*P. stomatis*、*F. nucleatum* 等可形成独特的细菌网络，并在 MSI 肿瘤患者中异常富集[72]，这提示该菌属对 CMS1 型 CRC 的治疗和预后更具潜力。

概括而言，消化链球菌属在 CRC 患者肠道中的定殖具有人群、空间、时间及分子亚型特异性，其分布模式不仅与患者体重指数及性别密切相关，还与肿瘤术后复发、化疗后骨髓抑制等临床结局高度相关；此外，该菌属在 CRC 不同空间位置、“腺瘤-癌”进展的不同阶段以及不同分子亚型间的丰度也存在显著差异(图 2，表 1)。

表1 消化链球菌在CRC中的相关研究

Table 1 Studies investigating the association between *Peptostreptococcus* and CRC

Research object	Research methods	Sample type	Major finding	Reference
25 healthy controls and 25 CRC patients; 54 healthy controls and 74 CRC patients; 1 healthy control and 1 CRC patient; 490 CRC	16S rRNA gene metagenome, qPCR immunohistochemistry (IHC), LC-MS	Fecal samples	In CRC patients, there is a notable increase in *Peptostreptococcus*, such as *P. stomatis*, *P. anaerobius*, and their tryptophan metabolites in the gut. Introducing microbial biomarkers improves the sensitivity of fecal immunochemical tests for detecting colorectal lesions	[46, 49-51]
275 CRC and 95 healthy controls	16S rRNA gene		*P. stomatis* was significantly enriched in patients with MSI-type CRC	[72]
35 healthy controls, 29 colorectal adenoma, 30 CRC; 61 healthy controls, 47 colorectal adenoma, 46 CRC	Metagenomics, 16S rRNA gene		Compared to the healthy control group and the colorectal adenoma group, the abundance of *P. anaerobius* increased sharply in CRC	[47,65]
589 CRC and data from published studies (4 439 CRC patients and controls)	16S rRNA gene		The association between *P. anaerobius* and CRC demonstrates strong robustness; it addresses two gaps in CRC microbiome research: quantifying microbiome traits related to cancerous colon changes and identifying microbial factors that may obscure true microbiome-CRC connections	[73]
522 CRC and healthy controls	Metagenomics, metabolome		*P. stomatis* shows a positive correlation with BMI in CRC patients; BMI criteria are specific to the Chinese population	[55]
12 CRC, 12 diabetes-CRC, 12 healthy controls	Metagenomics, targeted metabolome		The abundance of *Peptostreptococcus* is higher in patients with CRC complicated by diabetes	[56]
212 healthy controls and 212 CRC	PCR, PacBio		*P. anaerobius* is the most significant signature bacterium in male CRC	[57]
460 CRC (262 cases under 50 years old and 198 cases aged 50–88 years)	Shotgun metagenomics		The abundance of *P. stomatis* shows no significant difference across different age groups in CRC	[58]
41 treatment-naive CRC cases and 40 non-CRC controls	16S rRNA gene		The association between *Peptostreptococcus* and CRC is comparable between developed and developing countries	[59]
6 paired normal tissues, 20 paired CRC and adjacent normal tissues, as well as 2 additional unpaired tumors from 2 CRC patients	fluorescence *in situ* hybridization (FISH), 16S rRNA gene	Colon tissues samples	CRC tissues are enriched with invasive biofilms (particularly on right-sided tumors), which are composed of oral pathogens such as *P. stomatis*	[48]

(待续)

(续表1)

Research object	Research methods	Sample type	Major finding	Reference
32 CRC	16S rRNA gene, FISH qPCR, metagenomics metabolome	Colon tissues samples	*P. anaerobius* is significantly more abundant in CRC tumor tissues than in normal or adjacent non-cancerous tissues	[60]
34 CRC	16S rRNA gene, PCR	Colon tissues samples	Transcriptomic and metagenomic studies have associated the bacterial species *P. stomatis* with the CRC subtype CMS1	[36]
338 CRC	16S rRNA gene, qPCR	Mucosal samples	The *Peptostreptococcus* is enriched in advanced-stage CRC; a new gene mutation-based prognostic tool has been created to identify high-risk stage III CRC patients	[69]
13 096 CRC	Positive bacterial culture	Blood culture samples	*Peptostreptococcus*-related bacteremia increases CRC risk, suggesting microbiota-induced bacteremia as an early CRC warning	[42]
30 healthy controls and 93 CRC	16S rRNA gene	Saliva samples, fecal samples, subgingival fluid, tumor tissue	*Peptostreptococcus*, *Fusobacterium*, and *Parvimonas* are prevalent oral bacteria associated with CRC	[45]
51 healthy controls and 52 CRC	16S rRNA gene	Saliva samples, fecal samples	Local oral bacteria may have promoted the initiation of CRC carcinogenesis	[74]
Six cohorts comprising healthy controls and CRC patients; 98 CRC	qPCR, metagenomics IHC, FISH, 16S rRNA gene, LC-MS, fecal occult blood test (FOBT)	Saliva samples, fecal samples	The *Peptostreptococcus*, like *P. stomatis*, is enriched in CRC, and its abundance in both tumor mucosa and adjacent normal mucosa is higher than that in fecal samples	[39,62]
103 healthy controls, 32 colorectal adenoma, 99 CRC	16S rRNA gene	Oral swab, colonic mucosa, fecal samples	*P. stomatis* is linked to CRC, showing higher abundance in proximal tumor mucosa; a microbial biomarker classifier using oral and fecal microbiota effectively distinguishes CRC and adenomas from healthy individuals	[35]
Colon tissues from 96 CRC, 82 adenoma, and 77 healthy controls; fecal samples from 58 CRC patients and 54 healthy controls	qPCR, metagenomics 16S rRNA gene	Colon tissues, fecal samples	*P. anaerobius* levels are higher in CRC patients' fecal samples and increase from normal tissue to adenoma and CRC	[64]

3 消化链球菌影响CRC演进的作用机制

目前，尽管已有大量证据表明消化链球菌属在"口-肠轴"中的异常变化与CRC发生发展密切相关，但关于其与CRC的相关机制研究仍处于起步阶段。因此，本文基于现有报道总结消化链球菌属的致癌作用机制，包括促进肿瘤细

胞增殖、诱导上皮-间充质转化、重塑肿瘤微环境，为进一步的机制研究提供方向。

3.1 促进肿瘤细胞增殖

消化链球菌属可直接或间接通过细菌表面蛋白促进肿瘤细胞增殖，从而加速肿瘤进展。给予 $APC^{Min/+}$小鼠抗生素处理以清除内源性微生物后，连续灌胃 *P. stomatis*/*P. anaerobius* 可显著增加结直肠高度异型增生、腺瘤、腺癌的发生率[39-40]。体外研究发现，*P. stomatis* 以时间依赖性方式刺激 5 种人 CRC 细胞系增殖，且不影响正常结肠上皮细胞系生长；实验结果显示该菌可上调细胞周期标志物细胞周期蛋白 D1 (cyclin D1)和周期蛋白依赖性激酶 6 (cyclin-dependent kinases 6, CDK6)的表达，并抑制线粒体凋亡途径中的关键蛋白如半胱氨酸蛋白酶 7 (caspase-7)的切割形式，进而抑制 CRC 细胞凋亡并促进 G1-S 期进程[39]。进一步研究发现，细菌表面蛋白在促肿瘤细胞增殖中发挥关键作用。*P. stomatis* 通过 FBA 与 CRC 细胞上的整合素受体结合，激活 ERBB2-MAPK 信号通路，进一步增强细菌对癌细胞的黏附，并促进肿瘤细胞增殖[39]。此外，*P. anaerobius* 的表面蛋白同样可与 CRC 细胞上的整合素受体相互作用，激活 PI3K-Akt 途径中关键基因，包括 *Itga2*、*Akt1*、*Nfκb1* 等显著上调，并增加细胞增殖标志物[40]。由此可见，消化链球菌属表面蛋白的存在增加了其移位定殖于肠道的机会，也为后续参与 CRC 进展创造了先决条件。事实上，在 *F. nucleatum*、*P. gingivalis* 等常见口腔细菌中也发现了与消化链球菌属类似的表面蛋白/毒力因子，如黏附素 a、牙龈蛋白酶等，它们都属于细菌黏附素，可通过特异性结合宿主受体介导细菌黏附定殖，进而促进肿瘤细胞增殖[75-76]。然而，不同微生物所利用的黏附素种类、识别的宿主细胞受体及激活的下游信号通路各异。此外，另有研究指出梭杆菌属还能通过上调微小 RNA (microRNA)来增强 CRC 细胞的增殖和侵袭[77]。

3.2 诱导上皮-间充质转化

消化链球菌属可通过上调间质标志物与转录相关因子诱导肿瘤转移中的上皮-间充质转化(epithelial-to-mesenchymal transition, EMT)过程。EMT 是上皮细胞失去尖基底极性与邻近细胞建立联系，获得间充质表型并增强运动能力的过程[78]，这一生物学改变构成了肿瘤进展和转移的基础。研究发现 *P. anaerobius* 通过募集髓源性抑制细胞 (myeloid-derived suppressor cells, MDSCs) 并促进其分泌白细胞介素 -23 (interleukin-23, IL-23)诱导 MC38 细胞发生显著的间充质样梭形变化，同时增强 MC38 细胞的迁移和侵袭能力；此外，研究显示该过程伴随间质生物标志物 N-钙黏蛋白与转录因子 Snail、Slug、Twist 等表达上调[79]。相比之下，这种作用方式是消化链球菌属所特有的，目前并未在 *F. nucleatum*、*P. gingivalis* 等其余口腔微生物中报道，后者主要通过调节非编码 RNA 释放、促进外泌体介导的肿瘤相关基因跨生态位转移等途径诱导 EMT 并参与 CRC 转移[80-81]。此外，*P. anaerobius* 可分解色氨酸代谢物激活芳香烃受体，进而促进 CRC 发生[51]，而该受体的持续激活能下调 E-钙黏蛋白表达并促进肿瘤细胞迁移[82]，提示其潜在 EMT 调控作用。然而，该菌属调控 EMT 并促进转移的分子机制仍未完全阐明，进一步探索其在 CRC 转移中的功能靶点及信号通路不仅有助于揭示微生物-宿主互作的新机制，也将为开发基于微生物调控的靶向治疗策略提供理论依据。

3.3 重塑肿瘤微环境

肿瘤微环境(tumor microenvironment, TME)是由肿瘤细胞、免疫细胞及细胞外基质等组成的复杂生态系统，对 CRC 恶性进展至关重要。消化链球菌属可以募集肿瘤浸润免疫细胞，抑制抗肿瘤免疫反应的淋巴细胞，从而建立肿瘤允许的免疫微环境(图 3)。*P. anaerobius* 通过激活整合素驱动的 CRC 细胞中核因子 κB (nuclear

factor kappa-B, NF-κB)信号通路，释放趋化因子1 (chemokine ligand 1, CXCL1)与MDSCs上的跨膜受体相互作用，并促进MDSCs迁移到TME中，从而减少功能性$CD8^+$ T细胞的浸润[83]。进一步研究发现*P. anaerobius*不仅募集MDSCs进入TME[79]，还可分泌一种功能蛋白直接与MDSCs上的跨膜受体相互作用，促进精氨酸酶1 (arginase 1, Arg1)和诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)表达，从而赋予MDSCs免疫抑制活性并抑制$CD8^+$ T细胞免疫功能[83]。此外，肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)和肿瘤相关中性粒细胞(Tumor-associated neutrophils, TANs)也在CRC小鼠肠道中显著富集[40]。虽然*F. nucleatum*、*P. gingivalis*等口腔微生物也可募集肿瘤相关免疫细胞影响TME[84-85]，但消化链球菌属对MDSCS的双重调控机制是区别于它们的重要特征。消化链球菌属募集的这些异常免疫细胞具有病理激活性和极强的免疫抑制性，与CRC患者不良的临床预后密切相关[86]，提示其可作为CRC患者预后不良的生物标志物。

消化链球菌属还可增加TME中细胞因子如趋化因子、白细胞介素等表达，从而促CRC发生(图3)。*P. anaerobius*处理的CRC小鼠肿瘤组织中IL-23显著高于对照组[79]，提示该菌可能通过特定细胞因子通路参与CRC调控。体外研究证实，该菌还可上调Caco-2细胞中CXCL1的表达[83]。进一步研究发现，在$APC^{Min/+}$小鼠模型中灌胃*P. anaerobius*可导致白细胞介素-10 (interleukin-10, IL-10)、Ifng、Nfκb1等多个免疫相关分子表达上调[40]，引发细胞因子异常紊乱，并通过刺激慢性炎症和免疫逃避来促进癌症的发生和进展[87-88]，表明NF-κB通路的激活可能驱动促炎反应，并与CRC进展相关。尽管现有证据表明该菌属能够通过细胞因子重塑TME，但其确切机制尚未完全阐明，值得进一步探讨。

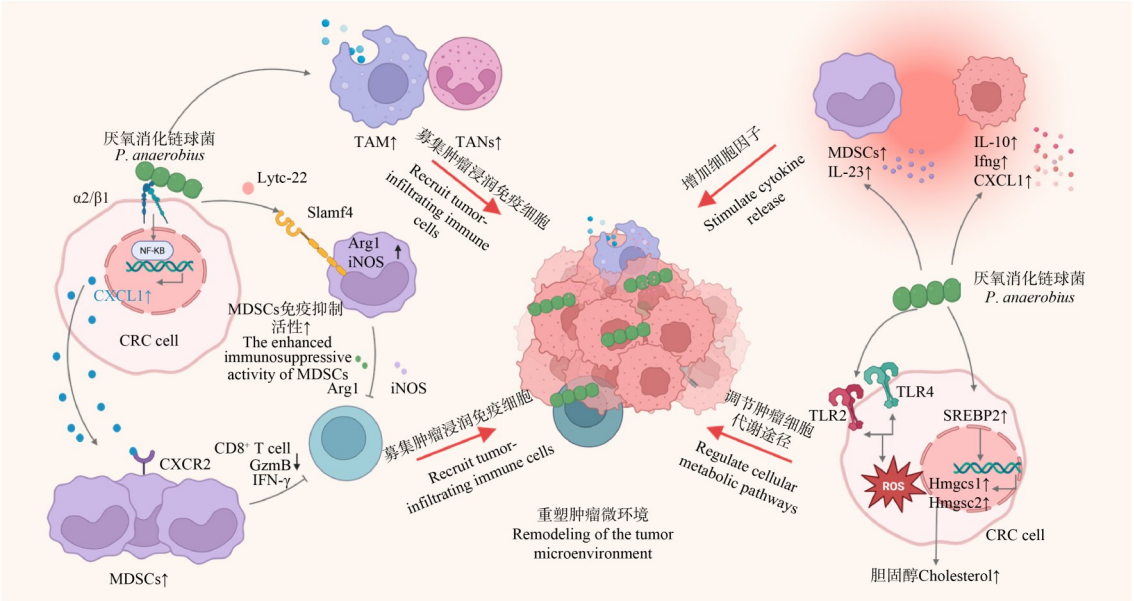

图3 消化链球菌对TME的影响

Figure 3 The effect of *Peptostreptococcus* on TME. TAM: Tumor-associated macrophage; TANs: Tumor-associated neutrophils; GzmB: Granzyme B; IFN-γ: Interferon gamma; CXCR2: c-x-c motif chemokine receptor 2; Slamf4: Signaling lymphocytic activation molecule family member 4; ROS: Reactive oxygen species; Hmgsc1: 3-hydroxy-3-methylglutaryl-coa synthase 1; Hmgsc2: 3-hydroxy-3-methylglutaryl-coa synthase 2.

肿瘤细胞最显著的特征是通过多种方式从营养匮乏的环境中高效摄取必需营养物质以维持其存活和增殖[89]。除了各种肿瘤浸润免疫细胞和细胞因子外，肿瘤细胞代谢途径也会影响TME (图 3)。与 *F. nucleatum* 影响肿瘤细胞糖代谢途径不同[84]，消化链球菌属主要经由胆固醇代谢途径影响 TME。Long 等[40] 对经 *P. anaerobius* 处理的人 CRC 细胞系进行基因集富集分析发现，该菌显著影响胆固醇稳态相关基因的表达。Tsoi 等[64]发现，暴露于 *P. anaerobius* 的人 CRC 细胞系中甾醇调节元件结合蛋白 (sterol regulatory element-binding protein, SREBP2) 及总胆固醇水平均显著升高，其中 SREBP2 是一种参与胆固醇生物合成和摄取的转录因子；在给予 SREBP2 抑制剂处理后，CRC 细胞内胆固醇水平下降，表明该菌通过 SREBP2 促进肿瘤细胞胆固醇合成；此外，该菌还可与 CRC 细胞上的跨膜蛋白 Toll 样受体 2/4 (Toll-like receptor 2/4, TLR2/4)相互作用，增加 CRC 细胞内活性氧水平从而增强胆固醇生物合成[64]。胆固醇代谢稳态失衡又会进一步促进瘤内微生物失调，为口腔微生物的移位定殖创造有利微环境，加速肿瘤恶化。

综上所述，消化链球菌属通过募集肿瘤浸润免疫细胞、抑制抗肿瘤免疫反应的淋巴细胞、促进细胞因子表达以及调节肿瘤细胞代谢途径重塑 TME (图 3)。尽管梭杆菌属和卟啉单胞菌属在驱动 CRC 进展方面具有类似作用，但消化链球菌属通过其对 MDSCs 的双重调控及对肿瘤细胞胆固醇代谢的特异性调节，在“口-肠轴”微生物与 CRC 关联中占据特殊地位。

4 挑战与展望

4.1 明确消化链球菌与 CRC 发生发展的因果关系

尽管消化链球菌属与 CRC 的联系已明确，但其中的因果关系仍有待阐明。“Alpha-bug”假说[90]强调，特定病原体通过破坏宿主微环境以及“排挤”益生菌来实现促癌效应；“Driver-passenger”模型[91]则认为，土著肠道微生物作为“驱动”因素可激发肠上皮细胞 DNA 损伤，为 *F. nucleatum* 等“乘客”细菌创造定殖条件，最终可能随 TME 变化被后者取代。虽然已有研究通过抗生素耗尽 $APC^{Min/+}$ 小鼠肠道微生物群[39-40]，来验证消化链球菌属可作为促 CRC 发生的要素，但该模型无法直接证明 CRC 相关消化链球菌的口腔来源，且由于动物模型与人类在微生物组结构及免疫系统方面存在显著差异，目前仍缺乏充分证据明确该菌属的失调是 CRC 的诱因、结果还是双向作用。因此，未来研究还需利用宏基因组和系统发育树分析，在菌株水平上对 CRC 患者配对的口腔与肿瘤样本进行分析，以确定来自 2 处位点的消化链球菌基因序列是否存在高度同源性和进化关联，并构建体外共培养模型、类器官平台及模拟口腔来源微生物经口传播定殖肠道的人源化动物模型等实验体系，进一步阐明口腔源性消化链球菌属与 CRC 发生发展的因果关系。

4.2 深入探究消化链球菌对 CRC 演进的作用机制

随着高通量测序技术的发展，消化链球菌属在 CRC 中的作用逐渐受到关注，但现有研究多为观察性分析，缺乏针对性的探索和强有力的机制证据。在上述总结及近期工作中发现，经“口-肠轴”传播的微生物似乎具有相似的传播方式及促 CRC 机制，这一现象虽需验证其与口腔来源的特异性关联，但为深入揭示消化链球菌属的作用机制提供了方向。(1) *P. gingivalis* 的耐酸性[92]可抵抗胃酸等宿主防御机制，其与 *F. nucleatum* 还可通过释放细胞外囊泡、脂多糖及菌毛等毒力因子促进肠道定殖[93]。鉴于消化链球菌属可经口-肠被动传输，可进一步探究其是否具备类似生物特性。(2) *F. nucleatum* 能诱导非编码 RNA 和宿主 DNA 损伤[94]，鉴于消化链球

菌属在 MSI 肿瘤患者中丰度显著升高，可验证其能否诱导遗传和表观遗传性病变从而促 CRC 发生。(3) 口腔细菌迁移至肠道后，其丰度的相对增加标志着其他肠道细菌的消耗[95]。鉴于消化链球菌属同其他口腔菌属在转移性 CRC 组织中富集[52]，并可增加肠道通透性[39]，可进一步验证该菌属是否通过直接调控肠道菌群结构影响肠道微生态以促 CRC 进展。同时，不同消化链球菌种/株在口腔和肠道微环境中可能存在营养、生态位竞争或代谢协同，这些相互作用对其各自丰度、毒力表达、在 CRC 的定殖能力及对整个口腔/肠道微生态的影响等尚不清楚，需实验验证。(4) *F. nucleatum* 可缓解 $CD8^+$ T 细胞的衰竭改善 CRC 免疫治疗效果[96]，而目前消化链球菌属的研究只停留在单向致癌作用，可进一步建立时空动态模型探索其是否在 CRC 进展及治疗预后中发挥双向调控作用。此外，现有研究多采用动物模型、肿瘤细胞/类器官-微生物共培养体系来探索“口-肠轴”微生物群和宿主在 CRC 进展中的相互作用，但难以完全模拟机体复杂环境。因此，未来研究应结合更可靠的疾病模型及前瞻性临床研究深入解析消化链球菌属在 CRC 发生发展中的作用。

4.3 拓展消化链球菌作为 CRC 微生物标志物的应用场景

虽然已有研究显示了消化链球菌属作为 CRC 生物标志物的潜力，但其临床应用仍面临样本选择、检测手段和数据分析等带来的诸多挑战。在样本选择上，当前 CRC 无创筛查主要依赖粪便隐血检测，但对早期病变敏感性低。口腔拭子可捕获以消化链球菌属为代表的 CRC 特征性菌群，其检测到的物种多样性显著超越传统粪便样本，同时联合粪便检测能明显提升鉴别 CRC 及息肉的灵敏度[35]，这一发现为开发兼顾筛查效能与患者依从性的“口-肠轴”多维诊断工具奠定生物学基础。在检测水平上，由于测序技术的局限性和菌株分选的挑战，目前的研究主要集中于菌属水平，未来应使用更高分辨率的微生物测序技术如单细胞转录组测序，同时结合新兴的空间多组学技术以从菌株或亚种水平全面评价消化链球菌属对宿主的影响。此外，该菌属的丰度在 CRC 进程中呈动态变化，设计实验时需综合考虑取样时机和部位等因素，构建动态监测模型，通过多时间点采样量化关键菌群在疾病不同阶段的特异性波动规律，同时应优化样本处理和测序方法降低宿主污染的影响。在数据分析上，Muller 等[97]通过引入“MintTea”有效解决了集成和分析复杂数据集带来的问题，成功验证了消化链球菌属与晚期 CRC 相关，证实人工智能驱动的大数据融合分析是破解微生物组复杂性的关键路径。

4.4 开发口腔源性微生物的针对性干预策略

针对消化链球菌属异常相关的 CRC，现有药物仅包括小檗碱[98]和多表位疫苗[99]。前者通过特异性抑制该菌属的氨基酸代谢通路来抑制其生长[98]；后者则是基于该菌属表面蛋白设计的亚单位疫苗，其通过诱导靶向抗体介导的免疫应答发挥抗肿瘤作用[99]。当前口腔源性微生物的新兴治疗策略如靶向细菌表面蛋白的合成抗菌肽[100]、基于基因工程改造噬菌体并联合纳米颗粒/脂质体等的递送系统[101]均可为靶向消化链球菌属的治疗提供方向。结合“口-肠轴”的特性，未来可探索“口腔菌群调控+肠道微生态重建”联合疗法，弥补传统治疗仅针对单一部位菌群的不足。例如，通过补充口腔益生菌，竞争性抑制致病菌在口腔的定殖，阻断其向肠道迁移的源头，同时实施粪菌移植(fecal microbiota transplantation, FMT)，选择富含益生菌且致病菌丰度低的供体菌群，重建肠道微生态平衡。此外，传统中药如半夏泻心汤也具有整体调控“口-肠轴”，减缓口腔微生物所促进的消化道疾病的潜力[23-24]。尽管口腔源性微生物在药物研发和药物载体方面具有潜在的应用价值，但其未知

副作用仍是亟待解决的关键问题，因此需结合更多的临床研究来评估其安全性及疗效。

5 总结

“口-肠轴”是理解人体微生物组如何系统影响宿主健康的重要切入点。近 10 年来，在理解“口-肠轴”失衡对 CRC 发生发展的影响方面取得了显著进展。本文探讨了口腔与肠道的微生物联系及其与 CRC 的关系，并具体分析了消化链球菌属与 CRC 发生发展的关联，总结了该菌属通过其表面黏附蛋白特异性定殖于肠黏膜，促肿瘤细胞增殖、诱导上皮-间充质转化并重塑 TME 的作用机制。此外，该菌属还有望作为 CRC 的诊断生物标志物及潜在治疗靶点。未来可将临床数据与人及动物的体内外研究结果相结合，利用先进的多组学技术进一步解析消化链球菌属在分子水平上影响“口-肠轴”进而促进 CRC 演进的机制及因果联系，开发兼具安全性与治疗精准度的微生物调节策略，为 CRC 的预防、诊断、治疗及预后提供新的切入点。

作者贡献声明

朱宇虹：文献检索、图表绘制、初稿撰写及修改；郭战丽：语言润色、核心内容的修订及补充；李雪珂：论文构思、框架设计、关键内容的审阅和修订；旷歧轩：提供核心理论与研究方向的关键性学术指导；付西：对论文整体方向与理论深度的学术指导；蒋义芳：提供研究视角与结果解读的关键指导和基金资助；马琼：负责格式规范及局部内容修订；由凤鸣：对结论有效性、文献引用准确性的审阅与修订；郑川：论文构思，对论文学术规范性、逻辑严谨性及全面性的审阅与修订。

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