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Review 综 述

链球菌-韦荣菌共生对系统性疾病的诊断价值研究

章聪[1]，徐硕[1]，徐伯麒[1]，周红光[2]，张军峰[1*]

1 南京中医药大学医学院·整合医学学院，江苏 南京 210023
2 南京中医药大学第一临床医学院，江苏 南京 210023

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摘　要：口腔是人体生理功能的窗口，也是种类和数量繁多的微生物库。口腔微生态变化能够反映宿主与环境因素的相互作用，进而影响机体健康和疾病的进展。其中，链球菌属(*Streptococcus*)和韦荣菌属(*Veillonella*)是口腔最早的定殖菌和典型共生菌，共同参与口腔早期生物膜形成。大量研究显示，链球菌和韦荣菌共生失调不仅与龋病、牙周病等口腔疾病密切相关，而且可突破或入侵消化屏障实现远端定殖，已经成为预测多种系统性疾病发生、发展及预后的新的潜在生物标志物。本文综述链球菌-韦荣菌在口腔的共生致病机制，分析其在系统性疾病相关微生态研究中的变化特征，提出具有代表性的共生菌诊断组合，以期为系统性疾病的诊断和防治提供科学依据。

关键词：链球菌；韦荣菌；共生；系统性疾病

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***Corresponding author.** Tel: +86-25-85811925; E-mail: zhangjunfeng419@njucm.edu.cn

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Diagnostic value of the symbiosis of *Streptococcus* and *Veillonella* in systemic diseases

ZHANG Cong[1], XU Shuo[1], XU Boqi[1], ZHOU Hongguang[2], ZHANG Junfeng[1*]

1 School of Medicine & Holistic Integrative Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China

2 The First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China

Abstract: Nurturing numerous microorganisms, oral cavity is the window into the physiological functions of the body. Oral microbiota is a mirror of the interaction between the host and environmental factors, which influences human health and disease progress. As the early colonizers of the oral cavity, the symbiotic *Streptococcus* and *Veillonella* contribute to the development of biofilm in human oral cavity. Mounting evidence suggests the key role of the symbiont in the development of many oral disorders, such as dental caries and periodontal disease. In certain state, they can also break through or invade the digestive barrier to colonize in remote organs, thereby affecting human health. They have been used as potential biomarkers for the occurrence, development, and prognosis of many systemic diseases. Thus, this paper reviewed the pathogenic mechanism of the *Streptococcus–Veillonella* symbiont, analyzed the characteristics of them in the microecosystem related to common systemic diseases, and proposed the representative diagnostic combinations, which would be expected to lay a scientific basis for the diagnosis and prevention of systemic diseases.

Keywords: *Streptococcus*; *Veillonella*; symbiosis; systemic diseases

口腔是人体生理功能的窗口，也是人体最大的微生物库之一，人类口腔微生物组数据库(human oral microbiome database，HOMD，Version 15.22，www.homd.org)显示来源于口腔分类群的细菌包括 12 门、24 纲、35 目、54 科、110 属、484 种(图 1 展示了相对丰度>1%优势菌群)，这些细菌主要分布在牙齿、龈沟、附着牙龈、舌、面颊、硬腭、软腭以及与口腔相邻的扁桃体、咽、食道、咽鼓管、中耳、鼻道和鼻窦、气管、肺[1]。其中，*Streptococcus* 和 *Veillonella* 是口腔优势菌属，具有较高的相对丰度，可达 19.2%和 8.6%[2]。变异链球菌(*Streptococcus mutans*)和远缘链球菌(*Streptococcus sobrinus*)等产酸链球菌与龋病相关[3]，而 *Veillonella* 能利用 *Streptococcus* 的糖代谢产物(例如乳酸)作为碳源，与之形成较为稳定的互利共生关系[4]，成为口腔疾病的潜在标志菌群。链球菌和韦荣菌共生是早期定殖菌形成口腔生物膜的前提和基础，揭示其在健康和患病人群口腔微生物组中的分布特征、变化趋势和作用机制，将为通过调节口腔微生态改善口腔环境和防治口腔疾病提供新的思路。

越来越多的证据显示，宿主免疫功能或饮食的改变可以改变口腔微生物组成和元转录组景观，增强细菌致病性；反过来，口腔微生物的代谢和诱导炎症反应可以促进局部菌群失调、相关的微生物丢失或过度增殖[5]。在健康人群中，口腔微生物传播并定殖到肠道中是普遍存在的。在口腔和肠道共享的 125 种细菌中，59%显示出沿消化道高频传播，包括 *Streptococcus* 和 *Veillonella* 等口腔核心菌群[6]。在病理条件下，易位的口腔菌群可作为紊乱群落中核心菌

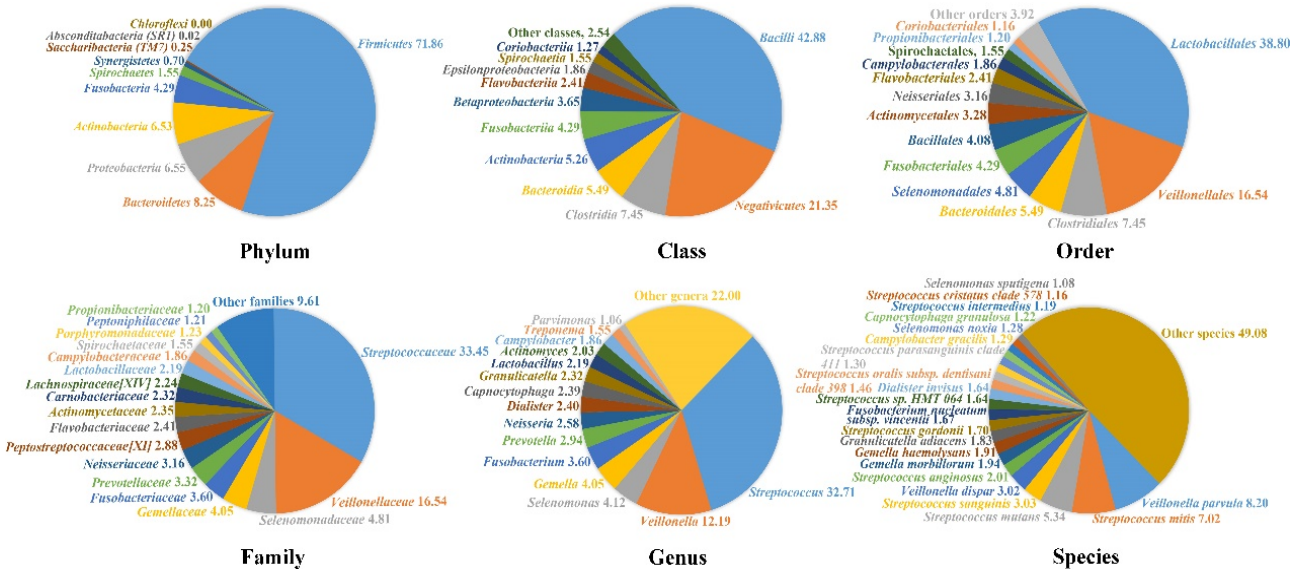

图 1　口腔细菌优势菌群群落结构

Figure 1　Community structure of dominant oral bacteria.

群发挥作用，与宿主交互作用推动免疫环境变化或整体疾病进程，如胃癌[7]、肝硬化[8]、炎症性肠病[9]等。病灶感染学说认为，口腔微生物可以通过病原体转移感染、毒素转移损伤和炎症因子转移性炎症，参与全身系统性炎症疾病的发生发展[10]，使得口腔菌群也成为心血管系统、神经系统、内分泌系统等非消化系统性疾病的标志菌群[11]。例如戈登链球菌(*Streptococcus gordonii*)可通过口腔损伤进入循环系统，与血管内皮细胞结合并在心脏瓣膜上积聚形成生物膜，引发感染性心内膜炎。一方面，定殖的戈登链球菌可诱导血小板聚集，形成细菌-血小板-纤维蛋白复合物来产生炎症反应；另一方面，戈登链球菌可直接激活由趋化因子募集的免疫细胞和刺激心脏瓣膜间质细胞产生细胞因子加剧炎症反应[12]。

1　链球菌和韦荣菌在口腔的分布特征

链球菌为革兰阳性菌，多兼性厌氧，HOMD 收录 33 个口腔链球菌种；韦荣菌为革兰阴性菌，专性厌氧，HOMD 收录 14 个口腔韦荣菌种。以 HOMD 菌种出现的丰度，展示前 10 个最常见的链球菌种和韦荣菌种(图 2)。

链球菌和韦荣菌在口腔中并非均匀分布，*Streptococcus* 在龈上斑块的丰度大于龈下斑块，而在非斑块部位的丰度明显高于斑块部位[13]。血链球菌(*Streptococcus sanguinis*)、戈登链球菌在无龋儿童牙菌斑中的相对丰度是患龋病儿童的 2 倍和 5 倍[14]。Doel 等[15]基于 16S rRNA 基因的一代测序发现了非典型韦荣菌(*Veillonella atypica*)的检出率为舌面>唾液>牙菌斑，殊异韦荣菌(*Veillonella dispar*)的检出率为舌面>唾液，小韦荣菌(*Veillonella parvula*)在牙菌斑中检出率最高。Kanasi 等[16]使用一代测序对 16S rRNA 基因测序显示非典型韦荣菌在龋病儿童牙菌斑中检出率高于健康儿童，而殊异韦荣菌、小韦荣菌无显著差异。Qudeimat 等[17]使用二代测序对 16S rRNA 基因 V3-V4 高变区测序发现龋病

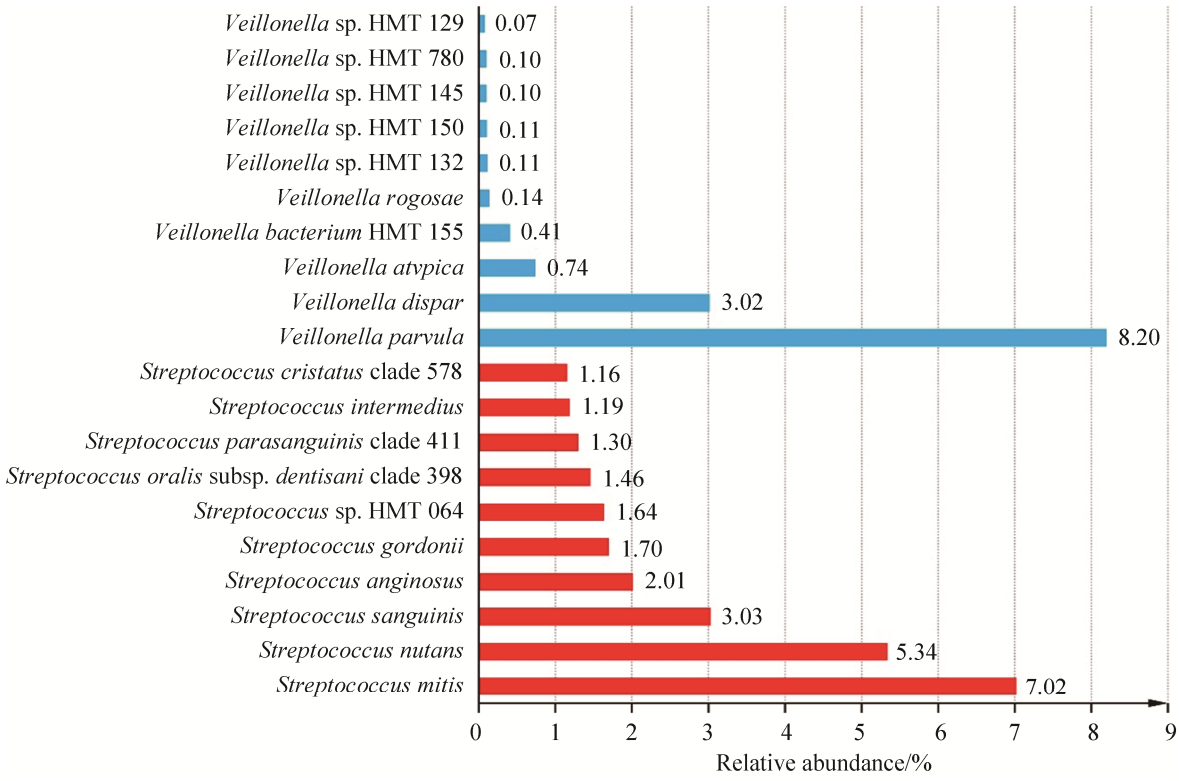

图 2　链球菌属与韦荣菌属中的优势菌种

Figure 2　Dominant species of *Streptococcus* and *Veillonella*.

儿童牙菌斑中殊异韦荣菌的相对丰度高于健康儿童。然而，Belstrøm 等[18]采用人类口腔微生物鉴定微阵列发现龋病成人唾液中非典型韦荣菌和小韦荣菌的检出率均低于健康人群。这种不一致的研究结果可能与受试人群、样本量大小、检测方法的敏感性和标本取样部位的差异相关。有研究发现，唾液中韦荣菌科(*Veillonellaceae*)和 *Veillonella* 的相对丰度与年龄呈负相关，*Streptococcus* 与年龄呈正相关，并且同卵双胞胎的唾液微生物比异卵双胞胎有更高的相似性[19]，Mukherjee 等[20]发现生活环境塑造口腔微生物组个性化能力强于遗传因素。这些研究结果提示，口腔微生物不仅受到口腔疾病的影响，还受到宿主年龄、生活环境、遗传等复杂因素的影响，即口腔菌群反映了宿主与环境的相互作用状态。

2　链球菌和韦荣菌的共生致病机制

链球菌和韦荣菌是重要的口腔早期定殖菌，通过糖代谢、信号交流、基因调节等多种方式建立稳定的共生关系，影响生物膜的形成和细菌的致病力(图 3)。*Streptococcus* 借助细胞表面粘附素(adhesin)与覆盖牙齿表面的唾液获得性薄膜(acquired pellicle)受体结合实现定殖，并与其他早期和晚期定殖菌共聚，特别是具有“桥梁”作用的 *Veillonella*[21−23] (图 3A)。变异链球菌可以产生至少 7 种酶来水解蔗糖为其他细菌提供糖代谢底物，分泌的葡萄糖基转移酶可催化产生一种具有黏性、相对不溶于水且富含 α-1,3 糖苷键的葡糖聚合物，成为致龋生物膜基质的关键组成部分，介导菌群黏附和包裹微生物形成复杂的细胞外聚合物(extracellular

polymeric substances，EPS)[24]。变异链球菌在合成葡聚糖过程中形成的游离果糖可以为*Veillonella*合成脂多糖(lipopolysaccharide，LPS)提供底物[25]。小韦荣菌的LPS可被人体细胞上的Toll样受体4 (Toll-like receptors 4，TLR4)所识别，通过丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)作用刺激单核细胞分泌细胞因子，引起宿主的免疫反应[26]，促进龋病等口腔疾病的发展(图3B)。

链球菌和韦荣菌以共聚集的方式建立信号交流，进而通过相互作用影响群落结构的发展(图3C)。韦荣菌不能进行糖代谢，必须依赖链球菌的糖代谢产物建立食物链。2种细菌通过群体感应(quorum sensing，QS)系统进行信号交流。链球菌和韦荣菌分别为革兰阳性菌和革兰阴性菌，其QS系统主要依赖自诱导因子-2 (autoinducer-2，AI-2)介导的信号通路，AI-2的生物合成途径高度保守，在许多革兰阳性菌和阴性菌中都存在AI-2的生物合成基因*luxS*及其同源基因，AI-2参与调控细菌致病性、运动性、生物膜形成和生物发光等[27]。Egland等[28]通过戈登链球菌和非典型韦荣菌共培养实验发现，非典型韦荣菌可能产生AI-2，诱导戈登链球菌编码α-淀粉酶的基因(*amyB*)的表达增强，加速

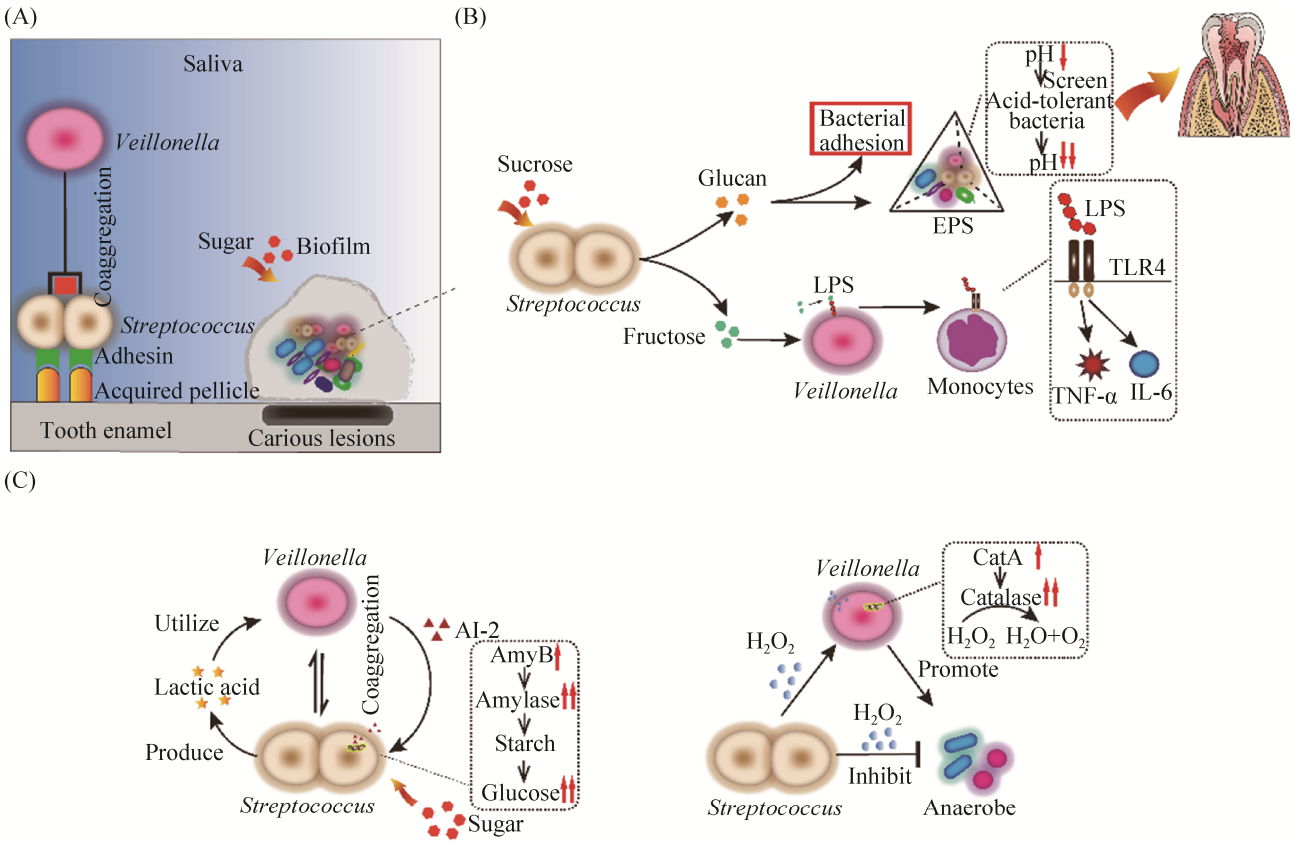

图3　链球菌和韦荣菌在口腔的共生致病机制

Figure 3　Symbiotic pathogenic mechanism of *Streptococcus* and *Veillonella* in oral cavity. A: early oral biofilm formation; B: symbiosis of *Streptococcus* and *Veillonella* mediates the occurrence of caries; C: signal communication between *Streptococcus* and *Veillonella*.

糖类的代谢。何智妍等[29]发现高表达 *luxS* 基因的变异链球菌与嗜酸乳杆菌共培养显示出更致密、集聚程度更高的生物膜。Mashima 等[4]发现当别町韦荣菌(*Veillonella tobetsuensis*)产生的 AI-2 可促进戈登链球菌生物膜的形成。此外，基于过氧化氢的化学信号交流影响群落结构的变化。*Veillonella* sp. PK1910 与口腔早期或晚期定殖菌共培养时，群落中的细菌都表现出快速增殖[30]，而韦荣菌种某些表达过氧化氢酶基因(*catA*)产生的过氧化氢酶则可以减缓由血链球菌和戈登链球菌产生的 H_2O_2 对厌氧菌的抑制作用[31–32]。

链球菌和韦荣菌作为口腔优势菌，致病性和保护性作用处于微妙的动态平衡，定殖菌种类和丰度可能成为影响口腔微生态的关键因素。致龋菌和非致龋菌的数量之间存在平衡，后者通过产生碱、过氧化氢或其他抑制物质来控制产酸致龋菌。频繁接触糖类会导致稳态的失衡，过量酸性物质的生成使耐酸菌—口腔链球菌(*Streptococcus oralis*)、戈登链球菌、变异链球菌[33]获得更多的竞争优势。口腔微环境的逐渐酸化，当 pH 值低于临界点 5.5 时，会导致牙釉质脱矿和牙齿表面形成空洞[34]。扩展龋病生态学假说(extended caries ecological hypothesis)认为，环境酸化可能推动微生物种群向特定表型和基因型菌株的毒性状态转变[35]。链球菌和韦荣菌在宿主体内的生态失调或易位定殖可能会引起多种疾病，而以其作为靶点以逆转生态失调和易位定殖为疾病治疗提供了新的视角。某些兼性和专性厌氧口腔细菌可将硝酸盐还原为亚硝酸盐进而生成一氧化氮，以调节血管张力和神经传递。一氧化氮产生的减少会对老年人血管张力和认知功能造成相关损害，而研究发现 *Streptococcus* 的丰度与血管健康标志物(高密度脂蛋白胆固醇和 ApoAI)水平呈正相关[36]，*Veillonella* 与唾液中的促炎代谢物和唾液白蛋白浓度相关[37]，以无机硝酸盐作为益生元饮食可以促进链球菌增加而韦荣菌减少，以改善年龄引起的心血管和认知健康障碍[38]。唾液链球菌 K12 菌株(*Streptococcus salivarius* K12)可以产生细菌素以抑制化脓性链球菌等细菌的生长；K12 菌株还具有免疫调节特性，通过抑制 NF-kB 途径、干扰 IL-8 合成和抑制 IL-8 分泌来下调炎症反应参与宿主防御过程，所以唾液链球菌 K12 菌株作为益生菌常用于治疗儿童分泌性中耳炎、病毒性咽炎等疾病[39]。对构成口腔微生物群落功能基础的细菌作用的深入了解，可能为发展新的方法调节口腔微环境以促进健康提供新的思路。

3 链球菌和韦荣菌对系统性疾病的诊断价值

大量研究显示，口腔疾病已经成为高血压[40]、阿尔茨海默病[41]、癌症[42]等慢性疾病的重要风险因素，提示口腔微生态失调以及引起的宿主内环境紊乱是导致全身系统性疾病的元凶之一[43–44]。近年研究发现，链球菌和韦荣菌在疾病和健康人群间具有显著差异，尤其是消化系统、呼吸系统和心血管系统疾病，已经显现出疾病诊断的潜在价值。

3.1 消化系统疾病

口腔是消化道的入口，唾液、胃酸、胆汁酸、消化酶等口腔-肠道屏障(oral-gut barrier)的天然存在，使细菌在口腔、胃、小肠、大肠等部位形成独特的微生态群落。当遗传、生活习惯、感染、癌变等因素影响口腔-肠道屏障时，会导致口腔菌群在消化道的异常变化[45]。近年来基于非依赖培养的高通量测序技术在人体微生态学研究中得到了广泛应用，本文聚焦常见消化系统疾病发生与链球菌-韦荣菌共生变化的相关性研究(表 1)。

表 1　消化系统疾病患者链球菌和韦荣菌的分布特征

Table 1　Distribution characteristics of *Streptococcus* and *Veillonella* in the patients with digestive system diseases

Diseases	Time	References	Country	Sample size	Samples	Methods	Results (relative abundance, P<0.05)
Oral squamous cell carcinoma	2019	Ganly I, *et al*. [47]	USA	18(OSCC)/ 8(PML)/ 12(HC)	Saliva	16S rRNA gene sequencing (V3–V4)	*Streptococcus*: HC (34.63%)>PML (22.30%)>OSCC (18.09%); *Veillonella*: HC (5.72%) <PML (14.86%)
	2018	Yang CY, *et al*. [48]	China	197(OSCC) /51(HC)	Saliva	16S rRNA gene sequencing (V3–V4)	*Streptococcus*: HC (35.57%)<OSCC (Ⅱ&Ⅲ) HC<OSCC(Ⅳ,28.21%); *Streptococcus mitis*: HC (31.86%)>OSCC (Ⅳ,19.65 %); *Streptococcus constellatus*: HC (0.22%)< OSCC(Ⅳ,2.18%); *Veillonella parvula*: HC (5.47%)>OSCC (Ⅳ, 3.36%)
	2017	Zhao HS, *et al*. [49]	China	40(OSCC)	Oral swab (cancerous lesions and neighboring noncancerous sites)	16S rRNA gene sequencing (V4–V5)	*Streptococcus*: noncancerous sites>cancerous lesions; *Veillonella*: noncancerous sites>cancerous lesions
Gastric cancer	2021	Huang K, *et al.* [55]	China	101(SG)/ 93(AG)/ 99(GC)	Saliva	16S rRNA gene sequencing (V3–V4)	*Streptococcus*: GC>SG, GC>AG
	2021	Horvath A, *et al.* [58]	Lithuania	14(GC)/ 8 (HC)	Feces	16S rRNA gene sequencing (V1–V2)	Gut *Streptococcus* and *Veillonella* increased after subtotal gastrectomy
	2020	Erawijantari PP, *et al*. [59]	Japan	50(GC)/ 56 (HC)	Feces	Shotgun metagenomic sequencing	Gut *Streptococcus* and *Veillonella* increased after subtotal gastrectomy
	2020	Wu J, *et al*. [57]	China	134(GC)/ 58(HC)	Feces	16S rRNA gene sequencing (V3–V5)	*Streptococcus mitis*: GC (0.37%)>HC (0.26%) *Streptococcus salivarius*: GC (2.77%)>HC (1.26%) *Veillonella*: GC (2.25%)>HC (0.78%)
	2019	Chen XH, *et al*. [7]	China	62(GC)	Gastric mucosa (cancerous lesions and neighboring noncancerous sites)	16S rRNA gene sequencing (V4–V5)	*Streptococcus*: noncancerous sites<cancerous lesions
	2018	Sun JH, *et al*. [56]	China	37(GC)/ 13(HC)	Subgingival plaque, saliva	16S rRNA gene sequencing (V4)	*Veillonella*: GC (22%)>HC (12%) in subgingival plaque
Inflammatory bowel disease	2018	Schirmer M, *et al*.[9]	USA, Canada	405(UC)	Rectum mucosa, feces	16S rRNA gene sequencing (V4)	*Streptococcus anginosus* had a 14-fold increase in the rectal mucosa in patients with severe UC compared to the mild; *Veillonella dispar* and *Veillonella parvula* tend to increase with the severity of the disease
	2018	Xun Z, *et al*. [63]	China	54(UC)/ 13(CD)/ 25(HC)	Saliva	16S rRNA gene sequencing (V3–V4)	*Streptococcus*: UC>HC; *Veillonella*: CD>HC
	2014	Gevers D, *et al*. [65]	USA	447(CD)/ 221(HC)	Ileum and rectum mucosa, feces	16S rRNA gene sequencing (V4) and Shotgun metagenomic sequencing	*Veillonellaceae*: CD>HC in mucosa and feces *Veillonella parvula*: CD>HC in feces
	2014	Said HS, *et al*. [64]	Japan	14(UC)/ 21(CD)/ 24(HC)	Saliva	16S rRNA gene sequencing (V1–V2)	*Streptococcus*: UC<HC, CD<HC; *Veillonella*: UC>HC, CD>HC

口腔癌是头颈部较常见的恶性肿瘤。其中，口腔鳞状细胞癌(oral squamous cell carcinoma，OSCC)占 90%以上[46]。Ganly 等[47]发现在唾液中 *Streptococcus* 的丰度沿健康人群(healthy control，HC)、癌前病变人群(premalignant lesions，PML)和 OSCC 的顺序逐渐减少，而 3 个牙周病原体(普雷沃菌属 *Prevotella*，拟普雷沃菌属 *Alloprevotella*，梭杆菌属 *Fusobacterium*)的相对丰度沿着 HC→PML→ OSCC 的顺序逐渐增加，并且三者呈现协同关系，共同抑制 *Streptococcus* 增殖；而 *Veillonella* 仅在 PML 中相对丰度显著增加，OSCC 与 HC 无显著差异。口腔菌群是随着 OSCC 癌症进展而变化的。在属水平上，OSCC Ⅱ期到Ⅳ期患者唾液中 *Streptococcus* 较 HC 减少；在种水平上，OSCC 各期患者唾液中星座链球菌(*Streptococcus constellatus*)较 HC 增加，尤其Ⅳ期患者中增加最明显，轻型链球菌(*Streptococcus mitis*)在肿瘤Ⅱ期到Ⅳ期患者中较 HC 减少，小韦荣菌在肿瘤各期患者中均减少，提示微生物群落中菌群丰度的变化可能与癌症病理分期有关[48]。Zhao 等[49]分析了 OSCC 患者癌组织和癌组织周围正常部位口腔拭子的微生物组，发现癌组织细菌多样性明显高于正常部位，*Streptococcus* 和 *Veillonella* 在癌变部位显著减少。然而也有研究发现，OSCC 患者唾液中 *Streptococcus* 比癌组织更丰富[50−51]，提示样本来源是导致研究结果不一致的重要原因，取样方法与部位的一致性有利于保证研究的重现性。

胃癌(gastric cancer，GC)是我国消化道最常见的恶性肿瘤，死亡率排恶性肿瘤第二位，较小规模的人群研究发现牙周病、牙齿脱落等可能与胃癌风险相关[52−53]，口腔卫生较差的人群中胃癌的发病率更高[54]，提示口腔微生物与胃癌的发生发展相关。胃癌的发展是一个多步骤过程，Correa 级联反应是目前公认的胃癌发病模式，认为正常胃黏膜经历了从浅表性胃炎(superficial gastritis，SG)、萎缩性胃炎(atrophic gastritis，AG)、肠上皮化生(intestinal metaplasia，IM)、上皮内瘤变(intraepithelial neoplasia，IN)到胃癌的逐步组织学阶段。在胃癌的演变过程中，口腔微生物可能由生态平衡向生态失调状态转变，表现为促炎性菌群的增殖或过度表达、微生物易位等。与健康人群或良性病变患者相比，胃癌患者的唾液或牙菌斑中 *Streptococcus* 和 *Veillonella* 具有较高丰度，这 2 个菌属作为生物标志物在诊断胃癌上具有较高的敏感性[55−56]。胃癌的癌性和非癌性组织的黏膜微环境中，微生物在组成结构、相互作用网络和功能上同样具有差异。*Streptococcus* 在癌组织中异常增殖，并与多种促炎菌共生以影响胃癌肿瘤微环境的发展[7]。Wu 等[57]研究发现轻型链球菌、唾液链球菌和 *Veillonella* 易位胃癌患者肠道并增殖，成为胃癌潜在的风险因素。手术治疗目前仍是胃癌根治的唯一手段，然而手术治疗不可避免地导致胃肠道发生严重的解剖和生理变化，包括胃肠道 pH 值、氧气供应、食物运输时间、肠道运动、消化液分泌等。与健康人群相比，接受胃大部切除术的患者的粪便微生物中显示出口腔微生物(例如 *Streptococcus* 和 *Veillonella)* 的易位和增殖，可能导致术后患者肠道菌群的失调和肠道炎症的迁延[58−59]。应用微生物制剂促进胃癌患者术后肠道生态平衡的恢复，不失为一种新颖的治疗手段。Zheng 等[60]开展的一项应用益生菌制剂治疗胃癌患者术后肠道功能紊乱的随机试验中，益生菌制剂增加了肠道内拟杆菌属(*Bacteroides*)、栖类杆菌属(*Faecalibacterium*)、阿克曼菌属(*Akkermansia*)等益生菌的丰度，降低了 *Streptococcus* 等促炎菌的丰度，有助于缓解术后炎症和提高机体免疫力。

炎性肠病(inflammatory bowel disease，IBD)包括克罗恩病(Crohn's disease，CD)和溃疡性结肠炎(ulcerative colitis，UC)，宿主肠道共生微生物的不适当和持续的炎症反应是致病原因之一[61]。易位定殖的口腔细菌在某些情况下异常激活肠道免疫系统，将导致慢性炎症疾病[62]。Schirmer等[9]在研究了新发或初治UC儿童的肠道菌群，发现重症患者直肠黏膜中咽峡炎链球菌(*Streptococcus anginosus*)的丰度是轻症患者的14倍，殊异韦荣菌和小韦荣菌在重症患者肠黏膜和粪便样本中高于轻症患者，提示口腔细菌异常增殖与肠道炎症的严重程度有关。Xun等[63]研究发现与健康人群相比，*Veillonella* 在CD患者唾液中增加，而 *Streptococcus* 在UC患者唾液中增加。与之不一致的是，Said等[64]研究发现，UC和CD患者唾液中 *Veillonella* 高于正常对照人群，而 *Streptococcus* 却降低。类似的，也有研究发现IBD患者肠道中 *Veillonella* 异常增殖和UC患者肠道中 *Streptococcus* 异常增殖[65–66]，提示疾病状态下，口腔和肠道微生物群在某种程度上是相互关联的。

3.2 呼吸系统疾病

口腔细菌的吸入是肺微生物群的最可能来源，并与吸入性肺炎[67]、慢性阻塞性肺病[68]等呼吸系统疾病相关，尤其是肺癌(表2)。肺癌患者口腔、气管、癌组织的微生物组与健康人群或良性病变患者存在差异。Leng等[69]研究发现肺鳞状细胞癌(lung squamous cell carcinoma，LSCC)患者痰液中 *Streptococcus* 和 *Veillonella* 丰度高于肺腺癌(lung adenocarcinoma，LAC)和HC。Wang 等[70]研究发现，LSCC 的肺泡灌洗液中 *Veillonella* 高于HC，小细胞肺癌(small-cell lung cancer，SCLC)的唾液中 *Streptococcus* 丰度高于 HC，肺泡灌洗液和唾液中细菌的构成相似。Yan等[71]研究发现，与HC相比，*Veillonella* 在 LSCC 和 LAC 唾液中都增加，而 *Streptococcus* 在LSCC唾液中减少。这些研究不仅分析了 *Streptococcus* 和 *Veillonella* 在肺癌和健康人群间的生态学差异，还探索了诊断早期肺癌、区分肿瘤组织类型的潜在诊断价值。Tsay 等[72]研究发现肺癌患者的下呼吸道富含 *Streptococcus* 和 *Veillonella*，与ERK和PI3K信

表 2 链球菌和韦荣菌在肺癌患者中的分布特征

Table 2 Distribution characteristics of *Streptococcus* and *Veillonella* in the patients with lung cancer

Time	References	Country	Sample size	Samples	Methods	Results (relative abundance, P<0.05)
2021	Leng QX, *et al*. [69]	USA	86(NSCLC)/89(HC)	Sputum	Droplet Digital PCR	*Streptococcus*: LSCC>HC, LSCC>LAC; *Veillonella*: LSCC>HC, LSCC>LAC
2019	Wang K, *et al*. [70]	China	18(LAC)/19(LSCC)/14(SCLC)/15(HC)	Saliva, bronchoalveolar lavage fluid	16S rRNA gene amplicon sequencing(V4)	*Streptococcus*: LC>HC in saliva and bronchoalveolar lavage fluid; SCLC(13.12%)>HC(9.20%) in saliva; *Veillonella*: LSCC (16.85%)>HC (7.17%) in bronchoalveolar lavage fluid
2018	Tsay JCJ, *et al*. [72]	USA	39(LC)/36(BPN)/10(HC)	Airway brushing	16S rRNA gene sequencing(V4)	*Streptococcus*: LC>HC, LC>BPN; *Veillonella*: LC>HC, LC>BPN
2015	Yan XM, *et al*. [71]	China	10(LSCC)/10(LAC)/10(HC)	Saliva	16S rRNA gene amplicon sequencing (V3, V6)	*Streptococcus*: LSCC<HC *Veillonella*: LSCC>HC, LAC>HC

* BPN: Benign pulmonary nodule.

号通路的上调有关，并在气道上皮细胞与产黑素普雷沃菌(*Prevotella melaninogenica*)、轻型链球菌、小韦荣菌体外共培养实验中验证了该信号通路，这提示 *Streptococcus* 和 *Veillonella* 可能通过上调 ERK 和 PI3K 信号通路促进肿瘤细胞增殖、存活和组织侵袭。痰和肺泡灌洗液是非侵入性获得的体液，含有来自肺和下呼吸道的支气管上皮细胞，因此可作为特异性诊断肺癌的新手段。中央型鳞癌常见于大气道或主支气管，痰液和肺泡灌洗液与这两个部位的分泌物相关，而周围型肺腺癌通常出现在周围肺组织中,起源于较远的小气道。与周围型腺癌相比，基于痰和肺泡灌洗液的分子生物标志物在识别中央型鳞状细胞癌上可能具有更高的敏感性。此外,痰或肺泡灌洗液的生物学检测与影像学检查相结合,将有助于弥补单一成像分析在早癌诊断的不足，提高肺鳞癌早期检测的敏感性。

3.3 心血管系统疾病

目前，*Streptococcus* 和 *Veillonella* 在心血管系统疾病中的研究较少。口腔链球菌、轻型链球菌感染常引发菌血症和感染性心内膜炎，可通过自身 *cdsA* 基因突变产生高度的耐药性[73]。动脉粥样硬化源于血管内膜胆固醇的积累和巨噬细胞的聚集。研究发现 *Streptococcus* 和 *Veillonella* 与动脉粥样硬化具有潜在联系，粥样硬化斑块中可以检测到 *Streptococcus* 和 *Veillonella*，且 *Streptococcus* 的丰度与高密度脂蛋白胆固醇和 ApoAI 水平呈正相关，*Streptococcus* 和 *Veillonella* 在口腔的丰度和动脉粥样硬化斑块中的丰度相关[36]。在患病人群的口腔和肠道微生物组中 *Streptococcus* 和 *Veillonella* 的相对丰度也较健康人群增加[74]。研究发现牙周病原菌的感染是动脉粥样硬化斑块发展的因素，在儿童期口腔感染可能是成人期患心血管疾病的风险因素[75]。

4 展望

口腔菌群通常以一定的协同作用以增强定殖能力、持久性或致病性，但其在口腔以外的共生致病机制亟待进一步研究阐释。非培养依赖的基于 16S rRNA 基因的高通量测序为研究口腔来源的共生菌在疾病发生发展过程中的变化提供了新的技术支持。当然，这些基于 16S rRNA 基因的非培养依赖的高通量菌群测序研究，还存在一些局限性：首先，最大局限就是无法区分死细菌和活细菌，导致获得的相对丰度存在较大的不一致性，成为应用于真实临床实践的巨大挑战；其次，目前的研究大多数停留在相关性研究，未能深入揭示口腔菌群对于宿主健康或疾病状态的影响；最后，易位出现的口腔菌群的生命状态缺乏研究技术和方法。近年来，宏基因组分析[76]、厌氧培养技术[77]、细菌空间单细胞转录组测序[78]、类器官[79]等方法为研究菌群功能状态提供了新的技术支撑，将极大推动菌群互作及其在宿主健康疾病过程中的功能，为人类重新认识口腔菌群参与健康与疾病的功能角色提供科学依据。

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