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· 基础研究 ·

牙源性上颌窦炎患者拔牙窝与上颌窦共有微生物谱的特征分析

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【摘要】目的 探讨牙源性上颌窦炎患者拔牙窝感染肉芽组织与上颌窦脓液在亚种-菌株水平是否存在共有微生物谱, 为牙源性上颌窦炎的感染溯源及精准抗菌治疗提供依据。**方法** 本研究已通过单位伦理委员会审查批准, 前瞻性纳入2020年10月至2022年8月接受全麻下同期鼻内镜手术及拔牙治疗的9例牙源性上颌窦炎患者, 采集拔牙窝感染肉芽组织及上颌窦脓液标本, 对16S rRNA进行Illumina MiSeq测序; 使用DADA2算法获得扩增子序列变体(amplicon sequence variants, ASV), 并以人类口腔微生物组数据库(human oral microbiome database, HOMD)注释至亚种水平。比较两部位共有ASV的检出率及其在上颌窦脓液中的相对丰度。采用通过重构未观察状态进行的群落系统发育分析工具第2版(Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2, PICRUS2)预测各样本宏基因组功能。**结果** 7例患者两部位存在共有ASV, 共有ASV以梭杆菌属、小单胞菌属、卟啉单胞菌属和普雷沃菌属最为常见; 其中, 牙龈卟啉单胞菌、具核梭杆菌在多位患者两部位共检出, 且在部分患者上颌窦脓液中的相对丰度>5%。6例患者存在具核梭杆菌或卟啉单胞菌属的同一ASV共检出; 具核梭杆菌具核亚种和牙髓卟啉单胞菌的对应ASV在上颌窦脓液中的丰度显著高于拔牙窝肉芽组织。PICRUS2功能预测提示, 上颌窦脓液中拔牙窝来源ASV占比与铁死亡、脂肪细胞因子信号通路、细胞凋亡等10条功能通路显著相关; 除生物素代谢外, 其余通路在拔牙窝肉芽组织中与上颌窦脓液中拔牙窝来源ASV占比相关性低。去除具核梭杆菌ASV后, 上述相关性明显减弱。**结论** 本研究在亚种-菌株水平证实牙源性上颌窦炎患者拔牙窝感染肉芽组织与上颌窦脓液之间存在共享的微生物谱, 上颌窦脓液中相对丰度较高的共检出亚种-菌株属于具核梭杆菌具核亚种和牙髓卟啉单胞菌, 为牙源性上颌窦炎感染溯源提供了菌株级微生物学证据。

【关键词】 牙源性上颌窦炎; 微生物迁移; 高通量测序; 具核梭杆菌; 卟啉单胞菌; 牙髓致病菌; 牙周致病菌; 16S rRNA

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Characterization of the shared microbial profile between infected extraction socket and maxillary sinus in patients with odontogenic maxillary sinusitis LU Chang¹, QIN Yicheng², WANG Ye¹, XU Min¹, LIN Jiang¹. 1.

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【Abstract】 Objective To explore whether infected granulation tissue in tooth extraction sockets and maxillary sinus pus share a common microbial profile at the subspecies-strain level in patients with odontogenic maxillary sinusitis (OMS), providing evidence for infection origin tracing and precise antimicrobial therapy in OMS. **Methods** This study was reviewed and approved by the institutional ethics committee. Nine consecutive OMS patients who underwent



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synchronous endoscopic sinus surgery and tooth extraction from October 2020 to August 2022 were prospectively enrolled. Under general anesthesia, paired specimens were collected from infected extraction-socket granulation tissue and maxillary sinus pus. Bacterial DNA was extracted, and the full-length 16S rRNA gene was sequenced on the Illumina MiSeq platform. Amplicon sequence variants (ASVs) were generated using the DADA2 algorithm and taxonomically annotated to the subspecies level against the Human Oral Microbiome Database. The detection rate of shared ASVs between the two sites and their relative abundance in sinus pus were compared. Functional profiles were predicted using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2 (PICRUSt2). **Results** Shared ASVs were identified in seven of the nine patients. *Fusobacterium*, *Parvimonas*, *Porphyromonas*, and *Prevotella* were the most prevalent genera. *Porphyromonas gingivalis* and *Fusobacterium nucleatum* were co-detected in multiple patients, with relative abundances exceeding 5% in sinus pus of several cases. Identical ASVs of *F. nucleatum* or *Porphyromonas* spp. were detected in six patients; the ASVs corresponding to *F. nucleatum* subsp. *nucleatum* and *Porphyromonas endodontalis* were significantly more abundant in sinus pus than in extraction-socket granulation tissue. PICRUSt2 functional profiling revealed that the proportion of socket-derived microbes in sinus pus was strongly correlated with 10 pathways, including ferroptosis, adipocytokine signaling, and apoptosis, et al. Except for biotin metabolism, the remaining pathways showed weak correlation with the proportion of extraction socket-derived ASVs in the extraction-socket granulation tissue and maxillary sinus pus. Removing *F. nucleatum* ASVs markedly attenuated these associations. **Conclusion** At the subspecies-strain level, this study confirmed the presence of a shared microbial profile between infected extraction-socket granulation tissue and maxillary sinus pus in patients with odontogenic maxillary sinusitis. The co-detected subspecies-strains with high relative abundance in maxillary sinus pus included *Fusobacterium nucleatum* subsp. *nucleatum* and *Porphyromonas endodontalis*, thus providing strain-level microbiological evidence for infection source tracing in OMS.

【Key words】 odontogenic maxillary sinusitis; microbial migration; high-throughput sequencing; *Fusobacterium nucleatum*; *Porphyromonas*; endodontic pathogens; periodontal pathogens; 16S rRNA

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牙源性上颌窦炎 (odontogenic maxillary sinusitis, OMS) 是一种细菌性鼻窦炎, 继发于邻近牙源性病变, 或继发于牙科手术并发症。OMS 约占所有慢性上颌窦炎患者的 50%^[1], 好发于 40~60 岁, 女性略多 (1.33: 1)^[2]。其鼻窦症状与非牙源性上颌窦炎相近, 不存在明确的特异性症状^[3], 但鼻塞等症显著更重^[4], 脓性分泌物比例显著高于非牙源性上颌窦炎^[5]。OMS 和其他慢性上颌窦炎的微生物文献 meta 分析显示^[6], 在种水平上, 具核梭杆菌是唯一在 OMS 患者上颌窦黏膜及脓液检出率高于 5%, 且 OMS 检出率显著高于非牙源性上颌窦炎的微生物; 在属水平上, 梭杆菌属也是唯一在 OMS 患者上颌窦黏膜及脓液检出率高于 5%, 且 OMS 检出率显著高于非牙源性上颌窦炎的微生物。

早期有研究者比较了两位点菌种的相似性^[7], 也有研究者比较了上颌窦和口腔的微生物菌门结构对比^[8]。然而, 这些研究多停留在“属”或“种”水平, 未能区分亚种/菌株, 也无法判定细菌究竟来

源于口腔还是上颌窦自身, 导致感染溯源始终停留在推论阶段, 更阻碍精准抗菌方案和潜在分子标志物的开发。随着第三代测序技术的发展, 长测序技术配合特征序列聚类的分析手法, 可以在亚种-菌株水平对微生物进行辨别^[9-10], 从而为上颌窦微生物溯源提供了更有力的研究方法。本研究旨在利用第三代高通量测序技术, 明确拔牙窝感染肉芽组织与上颌窦脓液之间共享的微生物谱, 并量化其在两部位的相对丰度, 从而在亚种层面系统阐明 OMS 患者拔牙窝与上颌窦之间微生物的对应关系, 为建立“菌株诊断+靶向抗菌”的精准诊疗策略提供微生物学证据。

1 资料和方法

研究已获得首都医科大学附属北京同仁医院伦理委员会批准 (审批号: TRECKY2020-138)。选择 2020 年 10 月至 2022 年 8 月于首都医科大学附属北京同仁医院就诊的 OMS 患者开展此课题的研究。

1.1 OMS患者诊断、纳入及排除标准

参考OMS专家共识^[11],纳入患者应符合上颌窦炎诊断和牙源性诊断标准,且耳鼻喉科医生和口腔科医生就牙周炎或根尖周病和鼻窦并发症之间的时间和病因关系达成一致。

1.1.1 上颌窦炎诊断标准 ①有鼻塞、流脓涕、嗅觉障碍和/或头痛等症状;②且/或鼻内镜检查发现中鼻道或嗅裂有脓性分泌物;③鼻窦CT检查提示窦腔黏膜有广泛或局限性炎症病变;以上对于上颌窦炎的诊断均由耳鼻喉科医生完成。

1.1.2 OMS感染来源判断 ①牙周来源:根据牙周炎病情需拔除患牙;患侧上颌牙附着丧失近根尖;锥形束CT(cone-beam computed tomography, CBCT)检查提示患侧上颌牙牙槽骨吸收达根尖,根尖与上颌窦底之间无骨质分隔。②根尖周来源:根据根尖周疾病病情需拔除患牙;患侧上颌牙无牙髓活力;CBCT检查提示患侧上颌牙根尖周低密度影,且根尖与上颌窦底之间无骨质分隔。③联合来源:如同时满足牙周来源和根尖周来源条件,则记为牙周-根尖周联合来源。以上对于OMS感染来源判断均由口腔科医生完成。

1.1.3 排除标准 ①术前30 d内有局部或全身急性炎症感染,术前2周使用抗生素;②术前确诊或疑似真菌性鼻窦炎、牙源性上颌窦囊肿、囊性纤维化、纤毛功能障碍、肿瘤、免疫缺陷;③孕妇及哺乳期患者;④年龄<18岁或>70岁的患者。

1.2 资料采集

1.2.1 临床资料采集 收集患者临床资料包括人口统计学信息、症状及手术史、专科检查、口内照片、CT及CBCT影像资料、拔牙后牙齿照片。

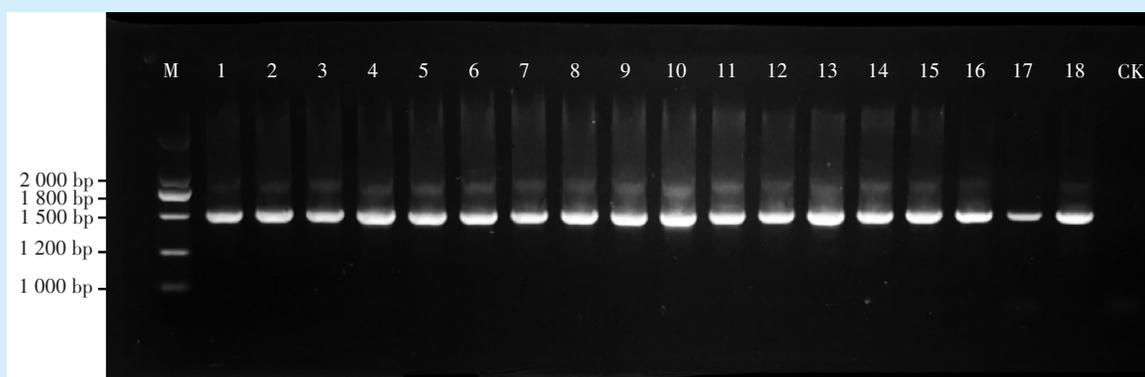
1.2.2 标本采集 所有病例均接受全麻下鼻内窥镜手术同期拔牙,患者仰卧位,在鼻内窥镜引导下使用无菌鼻拭子采集上颌窦内脓性分泌物,采集放入已编号冻存管后立刻存于液氮。取患侧上颌窦腔黏膜组织(尽量靠近上颌窦底),采集后放入已编号冻存管存于液氮,供后期制作病理切片。拔牙后同期收集拔牙窝感染肉芽组织(尽量靠近上颌窦),采集后同样放入已编号冻存管立刻存于液氮,供后期测序分析。

1.3 微生物分析

所有样本的微生物测序由北京奥维森公司进行,具体步骤如下。

1.3.1 样本基因组DNA提取及质量检测 蛋白酶K裂解法提取样本中细菌全基因组DNA,1.8%琼脂糖凝胶电泳检测样本DNA的浓度,聚合酶链式反应(polymerase chain reaction, PCR)预扩增检测样品是否合格。根据DNA质量检测结果,将各组符合要求的样本进行高通量测序分析。

1.3.2 PCR扩增和文库构建 利用细菌标准引物进行16S rRNA区域扩增,扩增后的产物进行质检,质检电泳图片如图1所示。



Lane M represents the DNA marker. Lanes 1 to 18 show PCR products from different samples. The presence of a distinct band in each lane, corresponding to the expected size, confirms successful amplification of the 16S rRNA gene. CK indicates the negative control without template DNA

Figure 1 Gel electrophoresis image after PCR amplification of the 16S rRNA region

图1 16S rRNA区域PCR扩增后质检电泳图

1.3.3 测序和数据优化处理 使用Illumina-Misq高通量测序平台对扩增产物进行测序。测序所得

的结果为原始数据,对其进行质量评估和优化处理。原始数据经FLASH双端Reads拼接,使用

Trimmomatic 进行过滤,去除低质量的碱基序列和模糊序列,之后使用 UCHIME 去嵌合体序列处理,所得优质序列进行后续分析。

1.3.4 代表序列生成和物种注释 使用 QIIME2 (版本 2021.2) 的 DADA2 算法通过统计模型识别并去除测序错误,推断出真实的扩增子序列变体 (amplicon sequence variants, ASV)。每个 ASV 代表唯一的序列变体。依据 HMD 中 16S rRNA 参考序列 (版本 15.23) 对 ASV 进行注释,比对参数设置为:序列一致性阈值为 0.77,查询序列覆盖度为 0.3,最大接受比对数为 1。得到特征序列的注释信息,将各样本测序数据按门、纲、目、科、属、种水平进行注释。使用 ClustalW 法绘制进化树。采用通过重构未观察状态进行的群落系统发育分析工具第 2 版 (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2, PICRUSt2) 依据京都基因与基因组百科全书 (Kyoto Encyclopedia of Genes and Genomes, KEGG) 数据库预测上颌窦脓液各样本宏基因组功能,最低比对率设为 0.6^[12]。采用 Spearman 秩相关分析,评估预测代谢通路与上颌窦脓液中拔牙窝来源 ASV 占比之间的相关性。

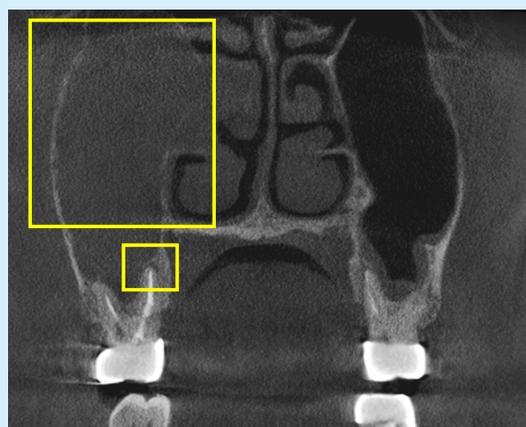
2 结果

2.1 患者基本特征与样本采集情况

研究共纳入 9 例患者,年龄 39~67 岁,包括 3 例男性,6 例女性。根据 OMS 专家共识^[11],经 CBCT 检查发现存在根尖周病变或严重牙槽骨吸收(吸收超过根长 2/3),且上颌窦窦底与病变分界骨板不连续,可认为牙齿为潜在感染源,6 例患者为根尖周来源,2 例患者为牙周来源,1 例患者为牙周-根尖周联合来源。在 9 例患者中,4 例具有牙痛症状。其中一个典型病例 (ID 号为 50),主诉为右侧鼻腔流黄绿色脓涕伴头痛 2 个月余。口内检查示右上颌第一磨牙 (#16) 全冠修复,牙周袋探诊深度为 3~9 mm,出血指数为 4,龈退缩 1~4 mm,近中、远中根分叉病变 II 度;叩痛(-),无松动。CBCT 示 #16 腭根根尖周低密度影,窦底骨质不连续,右侧窦口鼻道复合体软组织密度影,阻塞上颌窦开口(图 2)。2021 年 9 月 11 日行右侧筛窦-上颌窦开放术+中鼻甲部分切除+下鼻甲骨折外移+#16 拔除术。术中见拔牙窝与上颌窦腔贯通,大量黄白色脓液自窦口流出。病理回报右上颌窦黏膜慢性炎症。

2.2 测序数据概况

微生物测序共获得 59 729 个序列,每个样本



Cone-beam computed tomography demonstrates apical extension of a periapical radiolucency of the right maxillary first molar (#16), discontinuity of the sinus floor, and diffuse mucosal thickening with complete opacification of the right maxillary sinus (as indicated in the yellow boxes)

Figure 2 Representative imaging of a typical odontogenic maxillary sinusitis case from periapical periodontitis

图 2 根尖周来源牙源性上颌窦炎典型病例影像学资料

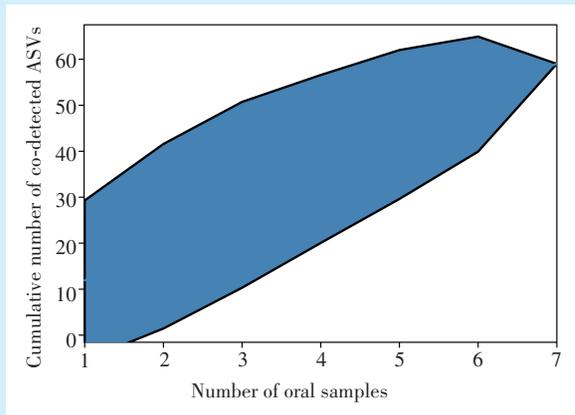
平均获得 6 636.6 个序列。共获得 1 589 个 ASV,长度中位数为 1 453 bp (25% 位数和 75% 位数分别为 1 441 bp 和 1 464 bp)。在拔牙窝肉芽组织与上颌窦脓液共检出 ASV 的累积曲线(图 3)显示纳入 7 例患者时曲线基本平坦,提示样本量基本满足研究要求。

2.3 共有 ASV 的属水平组成

如表 1 所示,9 例患者中,7 例患者有 ASV 在拔牙窝肉芽组织与上颌窦脓液共检出,在部分患者中,共检出 ASV 占上颌窦脓液 ASV 相对丰度超过 40%。小单胞菌属 (*Parvimonas*)、梭杆菌属 (*Fusobacterium*)、卟啉单胞菌属 (*Porphyromonas*)、普雷沃菌属 (*Prevotella*) 对应 ASV 在多例患者的拔牙窝-上颌窦共检出。如图 4 所示,将各患者两位点共检出 ASV 按对应属级分类标注后可见,卟啉单胞菌属 (*Porphyromonas*) 和梭杆菌属 (*Fusobacterium*) 在部分患者上颌窦脓液中具有较高的相对丰度。

2.4 共有 ASV 的种水平组成

进一步分析共检出 ASV 对应的菌种类型,如图 5 所示,牙龈卟啉单胞菌 (*Porphyromonas gingivalis*)、微小单胞菌 (*Parvimonas micra*)、具核梭杆菌 (*Fusobacterium nucleatum*) 等对应的 ASV 在拔牙窝肉芽组织与上颌窦脓液共检出较多,且在部分患者上颌窦脓液中相对丰度可超过 5%。



The x-axis represents the cumulative number of patient pairs (each pair includes infected extraction socket granulation tissue and maxillary sinus pus from the same patient); the y-axis shows the cumulative count of co-detected ASVs. The plateau indicates that the current sample size is sufficient to capture the full spectrum of shared ASVs. ASV: amplicon sequence variants. OMS: odontogenic maxillary sinusitis

Figure 3 Accumulation curve of 16S rRNA co-detected ASVs in granulation tissue in the extraction socket and maxillary sinus pus from patients with OMS

图3 牙源性上颌窦炎患者拔牙窝肉芽组织与上颌窦脓液中16S rRNA共检出ASV的累积曲线

2.5 关键菌株的系统发育一致性与丰度差异

系统发育分析(图6)进一步揭示,9例患者中,6例在拔牙窝肉芽组织与上颌窦脓液同时检出完

全一致的具核梭杆菌或卟啉单胞菌属特征ASV。其中,具核梭杆菌见于患者41、50、53;卟啉单胞菌属见于患者39、42、50、52。共检出节点在系统发育树中距离较近,提示共享菌株具有系统发育相关性。表2汇总了这些ASV的物种注释及丰度信息,结果显示具核梭杆菌具核亚种(*F. nucleatum subsp. nucleatum*)和牙髓卟啉单胞菌(*P. endodontalis*)的同一ASV在上颌窦脓液中的相对丰度明显高于拔牙窝。

2.6 功能预测结果及其与上颌窦中拔牙窝来源ASV占比的关联性

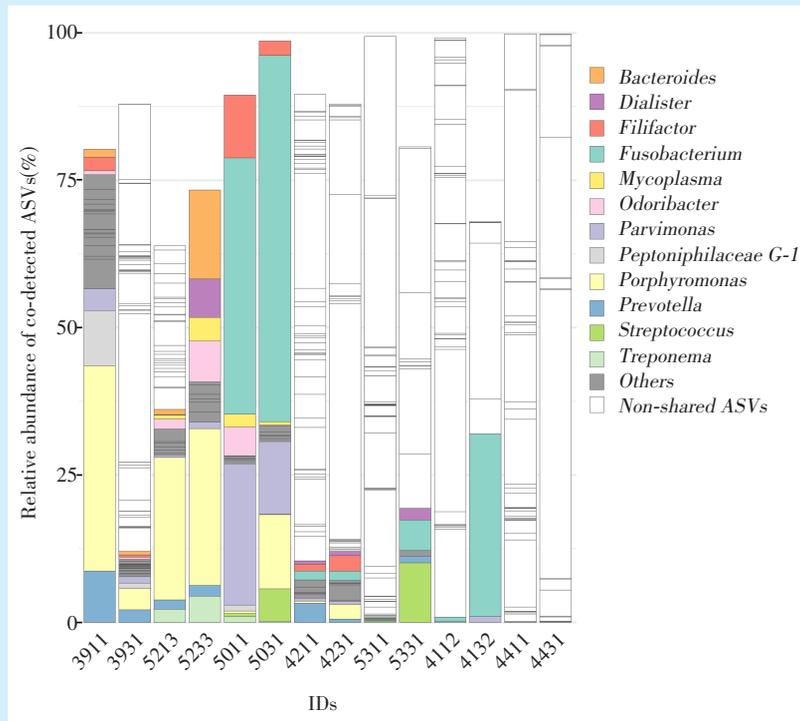
PICRUSt2功能预测显示,上颌窦脓液中拔牙窝来源ASV占比与多条代谢通路显著相关(表3、图7)。其中关联最强的前10条通路依次为铁死亡、脂肪细胞因子信号、细胞凋亡、细胞凋亡-果蝇、产热作用、过氧化物酶体增殖物激活受体信号通路(peroxisome proliferator-activated receptor signaling pathway, PPAR)、生物素代谢、硫胺素代谢、磷脂酰肌醇3-激酶-蛋白激酶B信号通路(phosphatidylinositol 3-kinase-protein kinase B signaling pathway, PI3K-Akt)及叶酸介导的一碳代谢。除生物素代谢外,其余通路在拔牙窝肉芽组织中与该占比的相关性均较低,提示其在上颌窦微环境中更为活跃。进一步剔除具核梭杆菌ASV后,上述通路的相关性显著下降,表明具核梭杆菌在塑造上颌窦微生物功能网络中可能发挥核心作用。

表1 牙源性上颌窦炎患者16S rRNA共检出ASV的属水平分布及相对丰度

Table 1 Genus-level distribution and relative abundance of ASVs co-detected via 16S rRNA sequencing in patients with odontogenic maxillary sinusitis

Patient ID	Age / years	Gender	No. of shared ASVs	Source	ASV Relative abundance in extraction socket (%)	ASV Relative abundance in maxillary sinus pus (%)	Co-detected genera (listed only if co-detected in at least three patients)
39	39	Female	35	Periapical	80.3	14.0	<i>Parvimonas, Porphyromonas, Prevotella, Filifactor, Odoribacter</i>
52	67	Male	26	Periodontal-Periapical	38.0	73.3	<i>Parvimonas, Porphyromonas, Prevotella, Dialister, Odoribacter</i>
50	41	Female	24	Periapical	92.9	98.6	<i>Parvimonas, Fusobacterium, Porphyromonas, Filifactor, Odoribacter</i>
42	63	Male	13	Periapical	11.3	14.0	<i>Parvimonas, Fusobacterium, Porphyromonas, Prevotella, Dialister, Filifactor</i>
53	62	Female	5	Periapical	0.7	19.3	<i>Fusobacterium, Prevotella, Dialister</i>
41	42	Male	4	Periodontal	1.3	43.1	<i>Parvimonas, Fusobacterium</i>
44	43	Female	1	Periapical	0.2	8.9	
38	65	Female	0	Periapical	0	0	
51	41	Female	0	Periodontal	0	0	

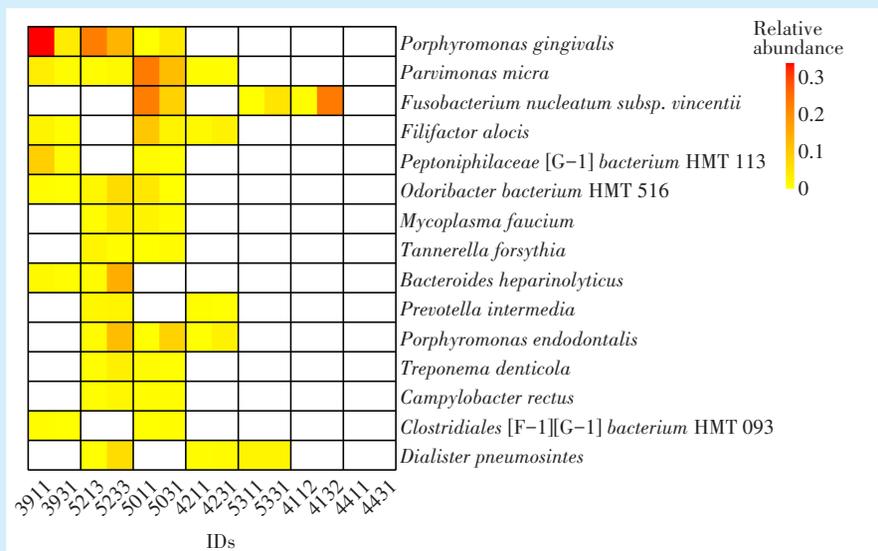
ASV: amplicon sequence variants



Genus-level classification and relative abundance of co-detected ASVs were analyzed by 16S rRNA sequencing. The x-axis shows sample IDs. Sample IDs: first two digits = patient ID; third digit = sampling site (1 = extraction socket, 3 = sinus pus); and fourth digit = infection origin (1 = periapical, 2 = periodontal, 3 = combined). OMS: odontogenic maxillary sinusitis. ASV: amplicon sequence variants.

Figure 4 Genus-level distribution of co-detected ASVs in extraction-socket granulation tissue and sinus pus from patients with OMS by 16S rRNA sequencing

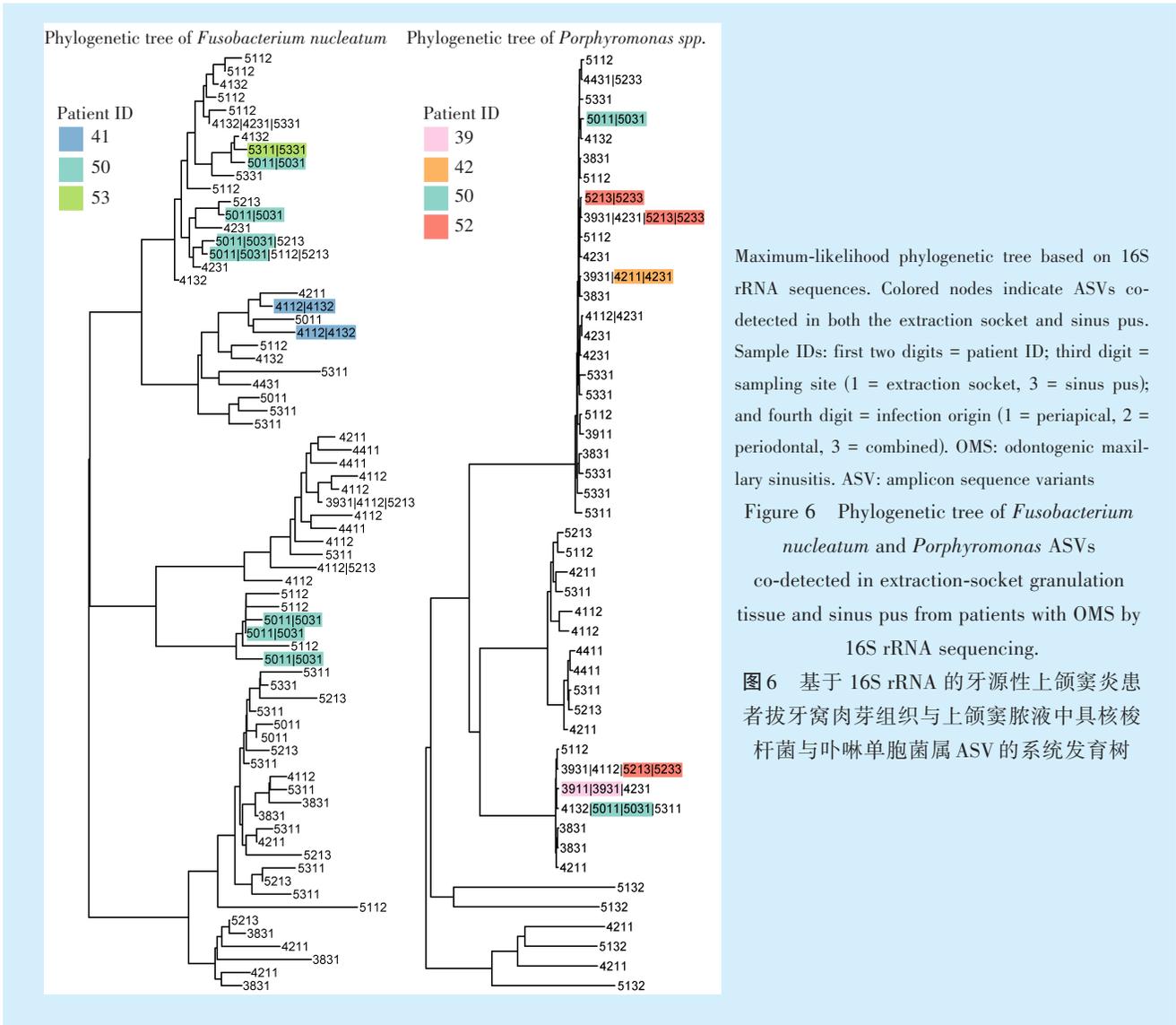
图4 16s rRNA 测序显示牙源性上颌窦炎患者拔牙窝肉芽组织与上颌窦脓液中共检出 ASV 的属水平分布



Only ASVs detected in at least two patient pairs are shown, ordered by mean relative abundance in sinus pus. Sample IDs: first two digits = patient ID; third digit = sampling site (1 = extraction socket, 3 = sinus pus); and fourth digit = infection origin (1 = periapical, 2 = periodontal, 3 = combined). OMS: odontogenic maxillary sinusitis. ASV: amplicon sequence variants. OMS: odontogenic maxillary sinusitis

Figure 5 Species-level distribution of co-detected ASVs in extraction-socket granulation tissue and sinus pus from patients with OMS by 16S rRNA sequencing

图5 16s rRNA 测序显示牙源性上颌窦炎患者拔牙窝肉芽组织与上颌窦脓液中共检出 ASV 的种水平分布



Maximum-likelihood phylogenetic tree based on 16S rRNA sequences. Colored nodes indicate ASVs co-detected in both the extraction socket and sinus pus. Sample IDs: first two digits = patient ID; third digit = sampling site (1 = extraction socket, 3 = sinus pus); and fourth digit = infection origin (1 = periapical, 2 = periodontal, 3 = combined). OMS: odontogenic maxillary sinusitis. ASV: amplicon sequence variants

Figure 6 Phylogenetic tree of *Fusobacterium nucleatum* and *Porphyromonas* ASVs co-detected in extraction-socket granulation tissue and sinus pus from patients with OMS by 16S rRNA sequencing.

图6 基于16S rRNA的牙源性上颌窦炎患者拔牙窝肉芽组织与上颌窦脓液中具核梭杆菌与卟啉单胞菌属ASV的系统发育树

3 讨论

本研究首次在亚种-菌株水平证实,OMS患者拔牙窝感染肉芽组织与上颌窦脓液之间存在共享的微生物谱,并定量分析了具核梭杆菌、牙髓卟啉单胞菌等关键致病菌的丰度,为“拔牙窝→上颌窦病原迁移”假说提供了关键微生物学证据。该结果不仅有助于精准溯源感染来源、指导个体化抗菌治疗,还为以具核梭杆菌为靶点的诊断标记物或治疗策略奠定基础,具备良好的临床转化前景:

①诊断层面:可在门诊或术中采用实时荧光定量PCR,针对具核梭杆菌具核亚种及牙髓卟啉单胞菌的特异性ASV进行检测,高度提示牙源性感染,减少不必要的广谱抗生素试验治疗。

②治疗层面:若具核梭杆菌占优势,可优先选用对革兰氏阴性厌氧杆菌敏感的硝基咪唑类(甲硝唑/替硝唑)联合β-内酰胺/酶抑制剂;若卟啉单胞菌属占主导,则推

荐阿莫西林-克拉维酸或莫西沙星等针对革兰氏阴性厌氧球菌的方案,避免“一刀切”给药。

既往研究已报道梭杆菌属、卟啉单胞菌属及普雷沃菌属在OMS患者上颌窦组织具有较高的相对丰度^[13-15],OMS微生物meta分析也显示梭杆菌属、卟啉单胞菌属在OMS组织中较高的检出率,特别是具核梭杆菌在OMS患者的上颌窦组织中的检出率显著高于其他类型的上颌窦炎^[6]。然而,直接比较口腔与上颌窦微生物相似性的研究较少,仅Brook等^[7]发现普雷沃菌属、卟啉单胞菌属、梭杆菌属及消化链球菌属在两位点共检出率较高。但上述文献均采用培养法或16S rRNA V3-V4区测序,而非16S rRNA全长测序,故对共检出谱的分析局限于属-种水平,不能支持亚种-菌株水平的上颌窦脓液-拔牙窝肉芽组织微生物共检出谱分析。此外,Lu等^[13]鼻窦炎取样采用的是中鼻道拭子,可能

表2 牙源性上颌窦炎患者拔牙窝肉芽组织与上颌窦脓液 16s rRNA 共检出具核梭杆菌及卟啉单胞菌属 ASV 及其相对丰度
Table 2 Shared ASVs assigned to *Fusobacterium nucleatum* and *Porphyromonas spp.* detected in granulation tissue in the extraction socket and sinus pus from patients with OMS with their relative abundances

Patient ID	ASV ID	Relative abundance in extraction socket (%)	Relative abundance in maxillary sinus pus (%)	ASV annotation
41	fe2db91dd3eeb9e1b749ad315bd96692	0.5	16.2	<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>
41	5437a73c0a999cb002f09d98448d1951	0.2	7.8	<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>
50	f243cb34918f37e0139103d999df850e	4.9	2.1	<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>
50	ac31ade967ef9f87452b3839c34db0a3	5.4	1.8	<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>
50	1680e420ed16d91da91c07bb9bc29ff6	6.4	3.7	<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>
50	bca23fd8016126a6804c4c88cdadf931	6.4	1.0	<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>
50	1b518e23ad28476e475e4caecc1efb95	4.6	10.9	<i>Fusobacterium nucleatum</i> subsp. <i>nucleatum</i>
50	03717b19b1a8774eb511d48e4b0f13e6	11.5	32.1	<i>Fusobacterium nucleatum</i> subsp. <i>nucleatum</i>
50	dd37d95f750d97c7c407daf19f433bb0	4.4	10.5	<i>Fusobacterium nucleatum</i> subsp. <i>nucleatum</i>
53	0eb6fce6dd352c822a8127df86aa5496	0.1	5.2	<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>
39	62fe71b8c566cc24a8c6a4b730f1f1d9	34.8	3.6	<i>Porphyromonas gingivalis</i>
42	5c90869902c98cae630dc4efdf837eb9	0.4	2.5	<i>Porphyromonas endodontalis</i>
50	a41f8585cbda55e9e45ab378f48faede	0.1	8.5	<i>Porphyromonas endodontalis</i>
50	e621b114e26af177eb3955de8aa2e9a4	0.3	4.1	<i>Porphyromonas gingivalis</i>
52	c6ceca35f79de11efdf507f1bc0be637	0.5	4.2	<i>Porphyromonas endodontalis</i>
52	867d35bec1cdb7a4c631c9681d08b92b	0.5	8.3	<i>Porphyromonas endodontalis</i>
52	62b2d5e99e68651fa093132b6b6fd8dc	23.1	14.1	<i>Porphyromonas gingivalis</i>

OMS: odontogenic maxillary sinusitis. ASV: amplicon sequence variants

表3 PICRUSt2 预测的代谢通路与上颌窦脓液中拔牙窝来源 ASV 占比的相关性分析

Table 3 Correlation between PICRUSt2-predicted metabolic pathways and the proportion of socket-derived ASVs in maxillary sinus pus

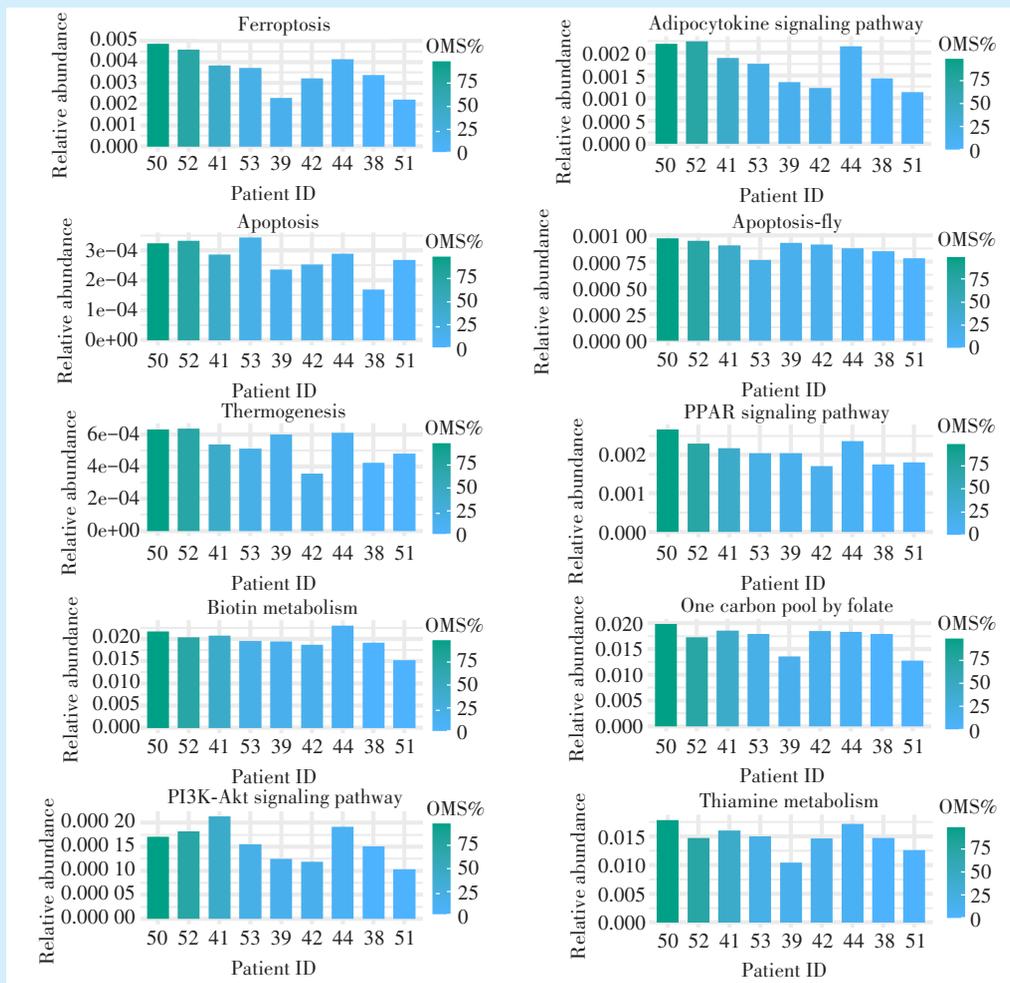
Metabolic pathway	Correlation in OMS pus (<i>r</i>)	Correlation in socket sample (<i>r</i>)	Correlation in OMS pus without <i>Fusobacterium nucleatum</i> (<i>r</i>)
Ferroptosis	0.72	0.19	0.32
Adipocytokine signaling pathway	0.71	0.10	0.12
Apoptosis	0.66	-0.49	0.13
Apoptosis-fly	0.66	-0.17	0.67
Thermogenesis	0.64	NA	0.05
PPAR signaling pathway	0.61	NA	-0.03
Biotin metabolism	0.57	0.67	0.31
Thiamine metabolism	0.54	0.54	N/A
PI3K-Akt signaling pathway	0.54	0.38	N/A
One carbon pool by folate	0.54	0.24	N/A

PPAR: peroxisome proliferator-activated receptor signaling pathway. PI3K-Akt: phosphatidylinositol 3-kinase-protein kinase B signaling pathway. OMS: odontogenic maxillary sinusitis. ASV: amplicon sequence variants. PICRUSt2: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2

难以捕捉某些局限于上颌窦内的口腔来源微生物。

参考 OMS 专家共识^[11], 本研究 9 例患者中, 6 例为根尖周来源, 2 例为牙周来源, 1 例为联合来源。既往文献多发现医源性因素为牙源性上颌窦

炎的首要致病因素^[3, 16-17], 其次为根尖周来源^[16], 再次为牙周来源。牙周炎为上颌窦黏膜增厚的危险因素^[18]。本研究未纳入拔牙后继发上颌窦炎患者, 入组患者以根尖周来源为主, 与既往报道一致。有必要说明, 患者来源于耳鼻喉科接诊确诊



Top 10 functional pathways most strongly correlated with the proportion of socket-derived ASVs in sinus pus, as predicted by PICRUSt2, along with their relative abundances. PICRUSt2: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2. ASV: amplicon sequence variants

Figure 7 Functional pathways associated with socket-derived ASVs in sinus pus from patients with odontogenic maxillary sinusitis

图7 牙源性上颌窦炎患者上颌窦脓液中拔牙窝来源 ASV 相关功能通路

为上颌窦炎,并经口腔科会诊证明上颌窦炎有根尖周或牙周感染,且 CBCT 显示根尖与上颌窦底之间无骨质分隔的患者,故患者并非一定具有口腔症状。实际上,对 OMS 诊断标准的描述为,患者应具有上颌窦炎相关症状(如鼻塞、流涕、面部压迫感、头痛、恶臭等),可伴有或不伴有口腔症状(如牙痛、牙齿松动、牙龈红肿等)^[11]。

OMS 依赖于多学科的诊断^[19],临床中未处理牙源性感染灶,单纯内镜鼻窦手术疗效较差^[20]。有研究报道上颌窦冲洗可辅助治疗 OMS^[21]。OMS 致病源于上颌后牙根尖或牙周感染灶与上颌窦底之间的解剖毗邻关系^[4, 22],窦底较薄是 OMS 的危险因素^[23]。随牙槽骨吸收或根尖病变进展^[24],窦

底骨板缺损为口腔厌氧菌提供了通道^[25],细菌通过骨裂隙、血管或淋巴途径侵入窦腔并定植,形成局部缺氧微环境及生物膜^[26],影响线粒体稳态,触发由中性粒细胞介导的急性炎症反应^[27],继而转化为以淋巴细胞和浆细胞浸润为主的慢性炎症^[28];持续的白细胞介素-1 等促炎因子释放^[21]导致窦黏膜弥漫性增厚及乳头状褶皱形成^[29],最终造成窦口阻塞和持续性上颌窦炎^[10]。

具核梭杆菌为经典牙周致病菌^[30],也与根尖周感染相关^[31]。具核梭杆菌在其他多种疾病中为机会致病菌,与呼吸道感染、炎症性肠炎、阴道感染、食道癌、结直肠癌等上皮病变相关^[32-33]。具核梭杆菌可以入侵上皮细胞,并可引发炎症^[34]。已

有文献列举的具核梭杆菌对上皮细胞的作用通路,包括核因子 κ B(nuclear factor kappa B, NF- κ B)通路、PI3K-Akt通路、p38/细胞外信号调节激酶-丝裂原活化蛋白激酶(p38/extracellular signal-regulated kinase-mitogen-activated protein kinase pathway, p38/ERK MAPK)通路等^[35]。另有研究表明具核梭杆菌的外膜囊泡可激活NF- κ B(p65)信号通路,进而激活NOD样受体家族含pyrin结构域蛋白3(NOD-like receptor family pyrin domain containing 3, NLRP3)炎症小体,上调白细胞介素-1 β 、白细胞介素-18、基质金属蛋白酶-2/9等炎症与组织降解因子^[36]。泛基因组研究提示,具核亚种较文森亚种携带更多与铁摄取及上皮黏附相关的毒力基因,并表现出更强的生物膜形成能力^[16,37],可诱导宿主细胞铁死亡^[38],这可能解释其在上颌窦脓液中的富集。

牙髓卟啉单胞菌为专性厌氧的革兰氏阴性菌,可在根尖周炎的感染根管^[39]及牙周袋内检出,且具有一定的迁移能力^[40]。牙髓卟啉单胞菌可诱导炎症因子产生,其毒力因子包括菌毛、荚膜、外膜蛋白、蛋白酶、代谢产物(如氨、硫化氢)、铁结合蛋白等^[41]。本研究部分患者以具核梭杆菌为主,另一部分以卟啉单胞菌属占优,与Lu等^[13]的发现一致。

微小单胞菌是一种存在于口腔、胃肠道、呼吸系统和女性生殖系统黏膜上的革兰氏阳性厌氧球菌,是一种“炎症嗜性菌”,即从炎症环境中获益并促进炎症持续^[42]。可促进Th17免疫细胞浸润和分泌白细胞介素-17、白细胞介素-22、白细胞介素-23等细胞因子,形成易于肿瘤发生的促炎环境^[43]。微小单胞菌可与具核梭杆菌等^[44]共聚集,促进生物膜形成,并促进牙龈卟啉单胞菌表达牙龈蛋白酶^[45]。有研究证实可从上颌窦炎患者上颌窦脓液中分离出具核梭杆菌和微小单胞菌^[46]。

上述微生物并非孤立致病。体外及动物研究证实,具核梭杆菌作为“桥梁菌”,通过表面黏附素与卟啉单胞菌、微小单胞菌共聚集,显著促进混合生物膜形成;其代谢产物丁酸、腐胺可加速卟啉单胞菌生物膜成熟-分散周期^[47]。共感染模型显示,具核梭杆菌与牙龈卟啉单胞菌协同放大白细胞介素-1 β 、肿瘤坏死因子- α 、基质金属蛋白酶-9表达,并促进NF- κ B核转位及细胞迁移^[48-49]。

本研究通过ASV级别的比对,在6例患者中鉴定到与HOMD亚种参考ASV 100%吻合、且在拔牙

窝肉芽组织与上颌窦脓液中同时检出的具核梭杆菌具核亚种及牙髓卟啉单胞菌特征ASV,首次在亚种-菌株水平证实了OMS两部位间存在共享病原体。然而,受16S rRNA基因片段分辨率及口腔微生物数据库完整性的限制,其余共有ASV仅能可靠注释至“种”或“属”水平,未能全部实现亚种-菌株水平的精确分类。

本研究具有以下局限性:①本研究为单中心前瞻性队列,仅纳入9例患者,其中仅7例检测到共有ASV,统计效能有限,可能遗漏低频或罕见微生物信号;②无法动态观察微生物迁移的时间序列,亦不能建立因果关系;③PICRUSt2结果需经宏基因组或转录组测序进一步验证;④未排除鼻中隔偏曲、鼻息肉等鼻腔病变,其微环境差异可能放大或掩盖口腔菌群信号;⑤未系统排除近期抗菌/免疫抑制用药,可能低估关键菌丰度,后续应排除或分层分析。

在今后的研究中,可以扩大样本规模,并设置非牙源性慢性上颌窦炎对照组,以提高结果的外推性和统计力度;另外,可在拔牙及鼻窦手术前后多个时点采集样本,结合同位素标记或体内示踪技术,直接证实微生物迁移方向及定植动态;还可以采用宏基因组、转录组及厌氧培养组学,深入解析具核梭杆菌等关键菌在上颌窦微环境中的致病毒力机制,并探索针对其毒力因子的精准干预策略。

综上,本研究证实OMS患者拔牙窝与上颌窦在亚种-菌株水平存在显著共享微生物谱,为牙源性感染溯源提供了新的微生物学线索。然而,尚无法直接证明“拔牙窝→上颌窦”的迁移过程。后续纵向研究、同位素标记或体内示踪试验将进一步阐明其方向性与动态变化。

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