四川大学学报（医学版） 2023，54（1）：54－60
J Sichuan Univ（Med Sci）

口腔微生物与慢性阻塞性肺疾病的关系*

杨红嘉[1]，张　正[2,3△]，王左敏[1△]

1. 首都医科大学附属北京朝阳医院 口腔科（北京 100020）；2. 天津市口腔医院 南开大学医学院（天津 300041）；
3. 天津市口腔功能重建重点实验室（天津 300041）

【摘要】 口腔微生物对宿主的疾病健康状态有着复杂的影响。研究发现肺部的菌群组成与口腔的菌群组成高度相似，且在慢性阻塞性肺疾病患者的痰液、支气管灌洗液中检测出口腔致病菌，提示口腔微生物在慢性阻塞性肺疾病的发生发展中发挥重要作用。大量研究结果表明，口腔微生物可能通过非特异性免疫反应、特异性免疫反应、蛋白水解酶的作用等途径参与慢性阻塞性肺疾病的发生发展。本文主要总结了口腔微生物与慢性阻塞性肺疾病之间关系的现有证据，通过研究两者之间的关系，阐明口腔微生物在诊断和预防慢性阻塞性肺疾病中的应用，探索未来可能的研究方向，为开发新的治疗方法提供参考。

【关键词】 口腔微生物　　牙周炎　　慢性阻塞性肺疾病

The Relationship Between Oral Microbiota and Chronic Obstructive Pulmonary Disease

YANG Hong-jia[1], *ZHANG Zheng*[2,3△], *WANG Zuo-min*[1△]. 1. *Department of Stomatology, Beijing Chao-Yang Hospital, Capital Medical University*, Beijing 100020, China; 2. *Tianjin Stomatological Hospital, School of Medicine, Nankai University*, Tianjin 300041, China; 3. *Tianjin Key Laboratory of Oral and Maxillofacial Function Reconstruction*, Tianjin 300041, China

△ Corresponding author, ZHANG Zheng, E-mail: zhangzheng@nankai.edu.cn; WANG Zuo-min, E-mail: wzuomin@sina.cn

【Abstract】 Oral microbiota have a complex impact on the host's health and disease states. It has been found that the composition of lung flora bears a striking resemblance to the composition of oral flora. Moreover, oral pathogenic bacteria have been detected in the sputum and bronchoalveolar lavage fluid of patients with chronic obstructive pulmonary disease (COPD), suggesting that oral microbiota play an important role in the pathogenesis and development of COPD. Findings from lots of studies have shown that oral microbiota may participate in the pathogenesis and development of COPD through non-specific immune response, specific immune response, and the activities of protein hydrolase. Herein, we mainly summarized the available evidence on the relationship between oral microbiota and COPD. By examining the relationship between the two, we elaborated on the application of oral microbiota in the diagnosis and prevention of COPD, discussed possible directions for future research, and provided references for developing new therapeutic approaches.

【Key words】 Oral microbiota　　Periodontitis　　Chronic obstructive pulmonary disease

慢性阻塞性肺疾病（chronic obstructive pulmonary disease, COPD）是一种具有高患病率、高致残率和高致死率特点的疾病，全世界每年有超过300万人死于COPD[1]。牙周炎能够显著增加COPD的发病风险，这一观点已被近年来开展的研究广泛报道。牙周炎是一种发生于牙周组织的感染性疾病，牙周炎患者的口腔中存在大量的致病菌，是人体细菌的重要聚集地之一[2]。研究发现肺部的菌群组成与口腔的菌群组成高度相似[3]，这提示口腔菌群的变化可能导致肺部菌群的改变。因此，牙周炎患者口腔微生物的变化可能影响肺部微生物的组成，诱发气道和肺组织炎症，从而影响COPD的发生发展。本文主要总结了口腔微生物与COPD之间关系的现有证据，通过研究两者之间的关系，探索未来可能的研究方向，阐明口腔微生物在诊断和预防COPD中的应用，并开发新的治疗方法。

1　牙周炎增加COPD发病风险的流行病学调查

大量流行病学证据表明牙周炎与肺功能降低有关。美国国家营养与健康调查发现：牙周袋探诊深度、附着丧失水平与肺功能指标1秒用力呼气量（forced expiratory volume in one second, FEV_1）、用力肺活量（forced vital capacity, FVC）、一秒率（FEV_1/FVC）呈负相关[4]。一项英国的横断面研究也发现：附着丧失水平、牙周袋探诊深度与肺功能指标FEV_1下降有关[5]，提示牙周炎越重的个体肺

* 国家自然科学基金（No. 82170956、No. 81870763）资助

△ 通信作者，张正，E-mail: zhangzheng@nankai.edu.cn；王左敏，E-mail: wzuomin@sina.cn

功能越差。也有研究表明牙周炎的严重程度与COPD的发病风险成正相关，重度牙周炎患者患COPD的风险是未患牙周炎、轻度至中度牙周炎患者的3.5倍[6]。一项来自于日本的横断面研究发现，COPD患病率在牙周炎患者中为12.7%，在非牙周炎患者中为7.8%[7]。而LOPEZ-De-ANDRÉS等[8]观察到，COPD患者的牙周病的发病率较非COPD患者增加了1.19倍，COPD住院患者的牙周病发病率较非COPD患者增加了3.17倍。CHUNG等[6]还发现，在COPD男性患者中，中度和重度牙周炎的患病率分别是非COPD男性患者的1.38倍和1.23倍。此外，口腔卫生保健措施也与COPD发病率有关，ZHUANG等[9]对512 715位30~75岁的中国人进行访谈发现从不刷牙的人COPD的发病率是其他人的1.12倍，而LIU等[10]也发现COPD急性加重频次越高的患者每天的刷牙时间越短。总的来说，牙周炎与COPD之间存在紧密相关性，COPD患者的口腔卫生状况及牙周状况均较非COPD患者的差，其原因之一可能是牙周炎增加了COPD的发生风险，还有一个原因可能是COPD影响了患者的口腔护理行为，但目前尚无文献报道COPD是否会影响患者口腔卫生保健措施的开展，未来我们还需更加深入的研究来论证这一观点。

2　口腔微生物在牙周炎影响COPD中的作用

口腔微生物是改变口腔乃至全身健康与疾病之间平衡的重要因素[11]。截至目前，学者们已在口腔中发现超过700种细菌、病毒、真菌等微生物物种[12]。健康状态下，口腔微生物处于动态平衡，但口腔卫生不佳、吸烟等因素会破坏口腔微生物之间的平衡关系，导致菌群失调，从而引起各种口腔疾病[13]。早在30年前，人们就认识到口腔微生物除了能够引发口腔疾病之外，还会造成机体远处部位的感染[14]。其中，学者们已在动脉粥样硬化患者硬化斑块中检测到口腔微生物的存在[15]。由于口腔与呼吸道相连续，健康成人在日常生活中也会吸入微量口腔微生物到呼吸道中[16]。这使得健康人群肺部的菌群组成与口腔的菌群组成高度相似，而与鼻腔的菌群组成相似度较差[3, 17-18]。此外，研究显示口腔微生物与肺功能之间存在关联，口腔菌群失调可能是COPD急性加重的危险因素[10]。这说明口腔微生物向肺部的迁移，可能会影响COPD病变过程。

除了口腔微生物能够迁移至肺部之外，多种呼吸道病原体也可定植于牙菌斑中[19]。PRAGMAN等学者[20-21]甚至将牙菌斑认定为COPD患者肺部微生物的储存库。健康状态下，这些微生物并不会引发呼吸道的炎症；但在COPD免疫受损状态下，微生物引起的宿主免疫反应就会对呼吸道产生破坏作用。对于牙周炎患者来说，牙周袋的形成为细菌的生长提供了良好的微环境。同时，牙周病原体产生的蛋白酶可以改变致病菌的定植环境，从而使更多的肺部病原体能够暂时定植于牙周组织中[22]。此外，牙周炎患者咀嚼、刷牙和牙周治疗等行为容易引起炎症牙龈组织的溃疡，造成口腔微生物穿过上皮屏障进入血液循环引起短暂的菌血症，并迁移至远隔的组织或器官，增加血行途径传播的风险[23]。然而目前尚无研究证实牙周微生物通过何种途径定植到肺部，未来还需要新的方法探索口腔微生物定植到肺组织的途径。

3　COPD患者肺部已被发现的口腔微生物

随着高通量测序技术在微生物检测方面的应用，越来越多的研究证实COPD患者肺部存在口腔微生物。截至目前，学者们已在COPD患者肺部发现的口腔微生物如下：

3.1　牙龈卟啉单胞菌

牙龈卟啉单胞菌（*Porphyromonas gingivalis*, *P. gingivalis*）是一种革兰阴性厌氧菌，也是牙周炎的重要致病菌之一[24]。MADALLI等[25]在COPD患者的气道分泌物中检测出*P. gingivalis*。*P. gingivalis*在COPD患者口腔中的检出率较非COPD患者显著升高，且其检出率与肺功能指标FEV_1呈负相关，提示COPD患者口腔菌群失调与肺功能下降有关[26]。

3.2　具核梭杆菌

具核梭杆菌（*Fusobacterium nucleatum*, *F. nucleatum*）是一种革兰阴性厌氧杆菌，也是一种常见的牙周病原体[27]。谭丽思等[28]通过对COPD急性加重患者的呼吸道分泌物进行检测，发现COPD急性发作患者呼吸道内存在*F. nucleatum*，且*F. nucleatum*相对含量随着肺功能的降低而增加，*F.nucleatum*与COPD患者急性加重的频率密切相关。

3.3　其他口腔微生物

元基因组分析发现COPD急性加重期患者的支气管灌洗液中可检测到牙周病原体（红色复合体、伴放线聚集杆菌等）[29]。一项病例对照研究显示，在COPD急性加重患者的呼吸道分泌物中，中间普氏菌的抗体水平显著升高[30]。体外实验发现，中间普氏菌培养液的上清液可以加强肺炎链球菌与下呼吸道上皮细胞的黏附，对小鼠肺炎链球菌感染有协同作用[31]。还有研究表明口腔微生物中需氧革兰阴性菌数量增加与气流阻塞的严重程度相关[26]。

4 口腔微生物参与COPD发生发展的机制

尽管诸多研究证明口腔微生物与COPD之间存在紧密相关性,但口腔微生物影响COPD发生发展的机制尚不明确。本文根据目前已发表的文献,总结口腔微生物参与COPD发生发展可能的机制如下:

4.1 非特异性免疫炎症反应

口腔菌群失调引起牙周炎,诱发宿主的局部和全身免疫反应。牙周组织的局部炎症导致多种炎症细胞因子如白细胞介素(interleukin, IL)-6、IL-1α、IL-1β、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和干扰素-γ(interferon-γ, IFN-γ)等进入循环,引起全身炎症性反应[32]。COPD 是一种累及气道、肺泡和微血管的渐进性炎症性疾病,气道炎症及全身炎症与COPD疾病进展及死亡率相关[33]。牙周炎引起的全身免疫反应可能会影响COPD的发生发展。有学者认为中性粒细胞可能是牙周炎和COPD的共同病理中心[34],中性粒细胞是炎症状态下的牙周组织中含量最丰富的白细胞,在口腔健康中发挥着重要作用[35]。本课题组前期研究发现:牙周炎患者牙周组织中的炎性细胞浸润比健康人更广泛,中性粒细胞的数量显著高于健康人[36];实验性牙周炎小鼠的肺组织中中性粒细胞较对照组小鼠浸润增多,且丝线结扎+牙周涂菌组的小鼠在第8周时肺组织中中性粒细胞浸润的数量较单纯丝线结扎组明显增多[37],这进一步证明了牙周微生物感染会进一步加重肺组织中中性粒细胞浸润。SAPEY等[38]检测了COPD患者外周血中中性粒细胞的趋化功能,发现伴牙周炎的COPD患者中性粒细胞迁移速度及准确率较不伴牙周炎的COPD患者明显下降。以上结果证明中性粒细胞在牙周炎与COPD之间起到重要作用,但具体的作用机制还需要更深入的研究。

4.2 特异性免疫反应

研究发现:COPD患者的肺气肿表现越明显,其支气管周围$CD4^+$ T淋巴细胞的浸润越多[39]。HUANG等[40]和Le ROUZIC等[41]认为辅助性T细胞17(T helper cell 17, Th17)在牙周炎和COPD之间发挥了重要作用。在健康状态下,Th17细胞产生保护性屏障反应,以维持口腔微生物与牙周组织之间的动态平衡;但当牙周组织受到病原体刺激时,Th17细胞是介导防御反应的免疫细胞[42-43]。同时,Th17细胞也是对抗肺部病原体的关键免疫细胞,它在许多肺部感染模型中介导免疫反应[43-46]。ZHENG等[47]通过免疫组化染色和流式细胞术对COPD稳定期患者、COPD急性加重期患者、吸烟者和不吸烟者的肺组织进行检测,观察到COPD稳定期患者肺组织中的Th17细胞数量是吸烟者的1.5倍,是不吸烟者的3倍;而COPD急性加重期患者肺组织中Th17细胞数量是吸烟者的2倍,是不吸烟者的5倍。

Th17细胞及其细胞因子促进牙周炎和COPD的发展。在特定条件下,Th17细胞及其分泌的细胞因子可加重肺组织中的慢性炎症[48]。Th17分泌的IL-17、IL-22与支气管上皮细胞上表达的相关受体结合,诱导中性粒细胞趋化因子和抗菌肽的产生[49-51]。IL-17刺激人支气管上皮细胞分泌碳酸氢盐和氯化物[49],在炎症状态下可以提高气道黏膜的抗菌能力[50]。IL-22通过诱导杯状细胞分泌黏液相关蛋白和促进上皮细胞增殖来保护组织[51]。同时,IL-17激活JAK-STAT信号通路,使牙周成骨细胞中核因子κB配体受体激活因子(receptor activator of nuclear factor κB ligand, RANKL)表达增加,从而加速破骨细胞分化[52]。不仅如此,分化后的Th17细胞直接激活RANK/RANKL信号通路,增强RANKL的表达,从而导致牙槽骨吸收[53]。Th17细胞在牙周炎和COPD中均起着重要的作用,未来我们或许可以以Th17细胞为突破口,进一步探索牙周炎与COPD的相互关系。

4.3 蛋白水解酶的作用

大量动物实验和细胞研究结果证明:中性粒细胞参与了COPD的发生发展,包括通过释放破坏性介质如中性粒细胞弹性蛋白酶(neutrophil elastase, NE)和基质金属蛋白酶(matrix metalloproteinase, MMPs)而导致的肺气肿等[54-55]。

NE是弹性蛋白、胶原蛋白和层粘连蛋白的有效降解剂[56]。NE在健康状态下发挥免疫作用,充当宿主的防御机制;但过度分泌的NE的蛋白水解作用会损害宿主组织[56]。一项前瞻性研究发现:C级牙周炎患者血清中NE的含量明显高于B级牙周炎患者[57],提示血清中NE的水平与牙周炎严重程度成正相关。ARAL等[58]也发现牙周炎患者龈沟液及唾液中NE水平均高于非牙周炎患者。另一项动物实验结果与其一致,HIYOSHI等[59]在小鼠实验性牙周炎中,发现龈沟液中NE的量与小鼠牙周附着丧失水平成正比,且NE抑制剂可减少丝线结扎导致的牙槽骨丧失量。在20世纪70年代,人们发现将NE注入动物肺部会造成实验动物肺气肿[60],COPD 患者的支气管肺泡灌洗液及肺组织中NE的浓度与肺气肿严重程度之间存在相关性[61-62]。炎症状态下,过量的NE将导致呼吸道黏液分泌增加、杯状细胞化生、囊性纤维化跨膜传导调节因子失活和细胞外基质重构,NE抑制剂可有效减少肺部炎症,现已取得良好的临床效果[56]。更多研究表明,中性粒细胞分泌的其他蛋白水解酶,如蛋白酶3和组织蛋白酶G,均

有可能诱导COPD[63]。

越来越多的学者开始关注MMP在牙周炎和COPD中的作用。MMP-8在炎症状态下可引起牙周组织和肺组织的结构破坏。YILDIRIM等[64]发现伴COPD的牙周炎患者血清中MMP-8、MMP-13比不伴COPD的牙周炎患者的显著升高。本课题组前期研究发现COPD频繁急性加重患者的唾液中MMP-8水平较非频繁急性加重的COPD患者显著升高[65]。SHARMA等[32]检测到伴COPD的牙周炎患者经过牙周基础治疗后唾液中的MMP-8水平较治疗前显著下降。牙周炎患者唾液中的MMP-8水平高于健康人[66],牙周基础治疗后唾液中MMP-8的水平显著降低,这表明它可用于监测牙周病的严重程度[32, 66]。COPD的病理生理学研究表明,MMP-8、MMP-2、MMP-9和MMP-12是降解肺实质及其细胞外基质的主要蛋白水解酶[67]。在COPD加重期间的患者痰中检测到MMP-8水平升高[68],且MMP-8与呼吸道阻塞有关[69],患有COPD的吸烟者的肺功能与唾液中的MMP-9水平呈负相关[70]。TRIPATHI等[71]将COPD患者外周血中性粒细胞在 LPS 刺激下培养24 h后发现MMP-9的表达水平显著高于非COPD患者。以上证据证实了MMP在牙周炎与COPD之间起到了不可忽视的作用,未来我们仍需更加深入的研究来探索其作用机制。

5　口腔微生物影响COPD治疗的疗效

本课题组前期研究发现:伴COPD的牙周炎患者牙周治疗1年后FEV_1和 FEV_1/FVC 水平均较治疗前显著升高,且2年内COPD急性加重的频率较未接受牙周治疗的患者明显降低[72]。KUCUKCOSKUN等[73]开展了一项前瞻性病例对照研究,将40名患有中度至重度牙周炎的COPD患者随机分为牙周治疗组和对照组,随访1年内牙周治疗组COPD急性加重的发病频率较对照组显著降低。SHEN等[74]基于台湾地区健康保险索赔数据进行了一项回顾性病例对照研究,发现定期进行牙周治疗的COPD患者在5年随访时间内死亡、COPD 急性加重、肺炎的发生率均较未行牙周治疗的COPD患者低。而在MADALLI等[25]的研究中,牙周治疗3~5个月后COPD患者痰液中牙龈卟啉单胞菌检出率从47%下降到27% 。牙周治疗可以减少口腔微生物在牙周组织中的定植,降低各种炎症因子的浓度,从而降低COPD急性加重的频率[34, 75]。另外,一些研究报道了使用超声波设备进行牙科治疗期间产生的气溶胶引起的细菌污染导致呼吸道症状恶化,建议在牙周治疗前使用抗菌漱口水、治疗过程中使用强力吸唾管等作为预防措施[76]。

6　展望

早期COPD没有症状或者症状轻微,容易漏诊,当患者出现明显症状并得到确诊时,患者肺通气功能损害往往已超过一半,失去了最佳治疗机会[77]。COPD 漏诊很常见,这意味着患者错失了通过最佳预防和治疗管理来减轻疾病负担的机会[78-79]。在中国以及世界其他地区,慢性阻塞性肺疾病的早期诊断和早期治疗都比较困难[77]。目前早期COPD的诊断主要包括肺功能测定、胸部断层扫描、强迫震荡技术等[80]。但在大部分国家和地区,呼吸科专家数量有限(尤其是在农村地区),先进诊断技术的费用昂贵,价格高昂的设备难以提供[77]。鉴于越来越多证据表明口腔微生物与COPD密切相关,检测微生物标记物已成为COPD辅助筛查与诊断的有希望的手段。

目前口腔微生物在COPD发生发展中的作用的研究仍较局限,仅局限于在COPD患者的气道分泌物中检测出口腔微生物、流行病学证据、牙周治疗影响COPD治疗效果等现象,还没有研究证据证实口腔微生物通过何种途径定植到肺组织,口腔微生物在COPD中的作用机制也尚不清楚,未来还需更多的研究继续探索口腔微生物在COPD发生发展中的作用途径及作用机制。

7　结论

综上所述,口腔微生物的菌群失调会导致肺部菌群失调,促进COPD的发生发展。未来的研究应侧重于阐明通过口腔微生物介导的COPD发生发展的详细机制。同时,随着测序技术的发展,利用口腔微生物作为COPD检测的生物标志物将成为可能。未来还需要更大规模、更全面的研究来验证口腔微生物对早期COPD的诊断价值,以制定更加精准的口腔微生物相关COPD防治策略。

*　　*　　*

利益冲突　所有作者均声明不存在利益冲突

参　考　文　献

[1] RABE K F, WATZ H. Chronic obstructive pulmonary disease. Lancet, 2017, 389(10082): 1931–1940. doi: 10.1016/S0140-6736(17)31222-9.

[2] AKKAOUI J, YAMADA C, DUARTE C, *et al*. Contribution of *Porphyromonas gingivalis* lipopolysaccharide to experimental periodontitis in relation to aging. Geroscience, 2021, 43(1): 367–376. doi: 10.1007/s11357-020-00258-1.

[3] BASSIS C M, ERB-DOWNWARD J R, DICKSON R P, *et al*. Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. mBio, 2015, 6(2): e00037. doi: 10.1128/mBio.00037-15.

[4] CHEN H R, ZHANG X F, LUO J, *et al*. The association between periodontitis and lung function: results from the National Health and Nutrition Examination Survey 2009 to 2012. J Periodontol, 2022, 93(6): 901–910. doi: 10.1002/JPER.21-0399.

[5] WINNING L, PATTERSON C C, CULLEN K M, *et al*. Chronic periodontitis and reduced respiratory function. J Clin Periodontol, 2019, 46(3): 266–275. doi: 10.1111/jcpe.13076.

[6] CHUNG J H, HWANG H J, KIM S H, *et al*. Associations between periodontitis and chronic obstructive pulmonary disease: the 2010 to 2012 Korean National Health and Nutrition Examination Survey. J Periodontol, 2016, 87(8): 864–871. doi: 10.1902/jop.2016.150682.

[7] HARLAND J, FURUTA M, TAKEUCHI K, *et al*. Periodontitis modifies the association between smoking and chronic obstructive pulmonary disease in Japanese men. J Oral Sci, 2018, 60(2): 226–231. doi: 10.2334/josnusd.17-0225.

[8] LOPEZ-De-ANDRÉS A, VAZQUEZ-VAZQUEZ L, MARTINEZ-HUEDO M A, *et al*. Is COPD associated with periodontal disease? a population-based study in Spain. Int J Chron Obstruct Pulmon Dis, 2018, 13: 3435–3445. doi: 10.2147/COPD.S174898.

[9] ZHUANG Z, GAO M, LV J, *et al*. Associations of toothbrushing behaviour with risks of vascular and nonvascular diseases in Chinese adults. Eur J Clin Invest, 2021, 51(12): e13634. doi: 10.1111/eci.13634.

[10] LIU Z, ZHANG W, ZHANG J, *et al*. Oral hygiene, periodontal health and chronic obstructive pulmonary disease exacerbations. J Clin Periodontol, 2012, 39(1): 45–52. doi: 10.1111/j.1600-051X.2011.01808.x.

[11] 王左敏. 口腔微生物组与全身疾病. 中国医刊, 2018, 53(7): 702–705. doi: 10.3969/j.issn.1008-1070.2018.07.002.

[12] CHEN T, YU W H, IZARD J, *et al*. The human oral microbiome database: a web accessible resource for investigating oral microbe taxonomic and genomic information. Database (Oxford), 2010, 2010: baq013. doi: 10.1093/database/baq013.

[13] ZAURA E, NICU E A, KROM B P, *et al*. Acquiring and maintaining a normal oral microbiome: current perspective. Front Cell Infect Microbiol, 2014, 4: 85. doi: 10.3389/fcimb.2014.00085.

[14] LAPORTE D M, WALDMAN B J, MONT M A, *et al*. Infections associated with dental procedures in total hip arthroplasty. J Bone Joint Surg Br, 1999, 81(1): 56–59. doi: 10.1302/0301-620X.81B1.0810056.

[15] LEISHMAN S J, DO H L, FORD P J. Cardiovascular disease and the role of oral bacteria. J Oral Microbiol, 2010: 2. doi: 10.3402/jom.v2i0.5781.

[16] GLEESON K, EGGLI D F, MAXWELL S L. Quantitative aspiration during sleep in normal subjects. Chest, 1997, 111(5): 1266–1272. doi: 10.1378/chest.111.5.1266.

[17] VENKATARAMAN A, BASSIS C M, BECK J M, *et al*. Application of a neutral community model to assess structuring of the human lung microbiome. mBio, 2015, 6(1): e02284-14. doi: 10.1128/mBio.02284-14.

[18] HUFFNAGLE G B, DICKSON R P, LUKACS N W. The respiratory tract microbiome and lung inflammation: a two-way street. Mucosal Immunol, 2017, 10(2): 299–306. doi: 10.1038/mi.2016.108.

[19] SCANNAPIECO F A, MYLOTTE J M. Relationships between periodontal disease and bacterial pneumonia. J Periodontol, 1996, 67(10 Suppl): 1114–1122. doi: 10.1902/jop.1996.67.10s.1114.

[20] PRAGMAN A A, KIM H B, REILLY C S, *et al*. The lung microbiome in moderate and severe chronic obstructive pulmonary disease. PLoS One, 2012, 7(10): e47305. doi: 10.1371/journal.pone.0047305.

[21] PRAGMAN A A, LYU T, BALLER J A, *et al*. The lung tissue microbiota of mild and moderate chronic obstructive pulmonary disease. Microbiome, 2018, 6(1): 7. doi: 10.1186/s40168-017-0381-4.

[22] ALMEIDA-Da-SILVA C, ALPAGOT T, ZHU Y, *et al*. Chlamydia pneumoniae is present in the dental plaque of periodontitis patients and stimulates an inflammatory response in gingival epithelial cells. Microb Cell, 2019, 6(4): 197–208. doi: 10.15698/mic2019.04.674.

[23] FORNER L, LARSEN T, KILIAN M, *et al*. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol, 2006, 33(6): 401–407. doi: 10.1111/j.1600-051X.2006.00924.x.

[24] OLSEN I, LAMBRIS J D, HAJISHENGALLIS G. *Porphyromonas gingivalis* disturbs host-commensal homeostasis by changing complement function. J Oral Microbiol, 2017, 9(1): 1340085. doi: 10.1080/20002297.2017.1340085.

[25] MADALLI R, KHEUR S, MAMATHA G S, *et al*. Assessment of role of *Porphyromonas gingivalis* as an aggravating factor for chronic obstructive pulmonary disease patients with periodontitis. Dental Hypotheses, 2016, 7(3): 100–106. doi: 10.4103/2155-8213.190485.

[26] TAN L, TANG X, PAN C, *et al*. Relationship among clinical periodontal, microbiologic parameters and lung function in participants with chronic obstructive pulmonary disease. J Periodontol, 2019, 90(2): 134–140. doi: 10.1002/JPER.17-0705.

[27] THOMAS C, MINTY M, VINEL A, *et al*. Oral microbiota: a major player in the diagnosis of systemic diseases. Diagnostics (Basel), 2021, 11(8): 1376. doi: 10.3390/diagnostics11081376.

[28] 谭丽思, 王宏岩, 赵海礁, 等. 呼吸道内具核梭杆菌与阻塞性肺疾病相关性研究. 中国实用口腔科杂志, 2013, 6(11): 664–667.

[29] TAN L, WANG H, LI C, *et al*. 16S rDNA-based metagenomic analysis of dental plaque and lung bacteria in patients with severe acute exacerbations of chronic obstructive pulmonary disease. J Periodontal Res, 2014, 49(6): 760–769. doi: 10.1111/jre.12159.

[30] WU X, CHEN J, XU M, *et al*. 16S rDNA analysis of periodontal plaque in chronic obstructive pulmonary disease and periodontitis patients. J Oral Microbiol, 2017, 9(1): 1324725. doi: 10.1080/20002297.2017.1324725.

[31] NAGAOKA K, YANAGIHARA K, HARADA Y, *et al*. Macrolides inhibit *Fusobacterium nucleatum*-induced MUC5AC production in human airway epithelial cells. Antimicrob Agents Chemother, 2013, 57(4): 1844–1849. doi: 10.1128/AAC.02466-12.

[32] SHARMA S, GUPTA A, VERMA A K, *et al*. Impact of non-surgical periodontal therapy on pulmonary functions, periodontal health and salivary matrix metalloproteinase-8 of COPD patients with chronic periodontitis: a clinico-biochemical study. Turk Thorac J, 2021, 22(4):

324–332. doi: 10.5152/TurkThoracJ.2021.20096.

[33] VOGELMEIER C F, CRINER G J, MARTINEZ F J, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. Am J Respir Crit Care Med, 2017, 195(5): 557–582. doi: 10.1164/rccm.201701-0218PP.

[34] USHER A K, STOCKLEY R A. The link between chronic periodontitis and COPD: a common role for the neutrophil? BMC Med, 2013, 11: 241. doi: 10.1186/1741-7015-11-241.

[35] VADIRAJ S, NAYAK R, CHOUDHARY G K, *et al*. Periodontal pathogens and respiratory diseases- evaluating their potential association: a clinical and microbiological study. J Contemp Dent Pract, 2013, 14(4): 610–615. doi: 10.5005/jp-journals-10024-1373.

[36] ZHANG Z, YUAN W, DENG J, *et al*. Granulocyte colony stimulating factor (G-CSF) regulates neutrophils infiltration and periodontal tissue destruction in an experimental periodontitis. Mol Immunol, 2020, 117: 110–121. doi: 10.1016/j.molimm.2019.11.003.

[37] TIAN H, ZHANG Z, WANG X, *et al*. Role of experimental periodontitis in inducing pulmonary inflammation in mice. Oral Dis, 2022, 28(8): 2294–2303. doi: 10.1111/odi.13949.

[38] SAPEY E, YONEL Z, EDGAR R, *et al*. The clinical and inflammatory relationships between periodontitis and chronic obstructive pulmonary disease. J Clin Periodontol, 2020, 47(9): 1040–1052. doi: 10.1111/jcpe.13334.

[39] SZE M A, DIMITRIU P A, SUZUKI M, *et al*. Host response to the lung microbiome in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2015, 192(4): 438–445. doi: 10.1164/rccm.201502-0223OC.

[40] HUANG N, DONG H, LUO Y, *et al*. Th17 cells in periodontitis and its regulation by A20. Front Immunol, 2021, 12: 742925. doi: 10.3389/fimmu.2021.742925.

[41] Le ROUZIC O, PICHAVANT M, FREALLE E, *et al*. Th17 cytokines: novel potential therapeutic targets for COPD pathogenesis and exacerbations. Eur Respir J, 2017, 50(4): 1602434. doi: 10.1183/13993003.02434-2016.

[42] DUTZAN N, ABUSLEME L, BRIDGEMAN H, *et al*. On-going mechanical damage from mastication drives homeostatic Th17 cell responses at the oral barrier. Immunity, 2017, 46(1): 133–147. doi: 10.1016/j.immuni.2016.12.010.

[43] GAFFEN S L, MOUTSOPOULOS N M. Regulation of host-microbe interactions at oral mucosal barriers by type 17 immunity. Sci Immunol, 2020, 5(43): eaau4594. doi: 10.1126/sciimmunol.aau4594.

[44] AUJLA S J, CHAN Y R, ZHENG M, *et al*. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med, 2008, 14(3): 275–281. doi: 10.1038/nm1710.

[45] UMEMURA M, YAHAGI A, HAMADA S, *et al*. IL-17-mediated regulation of innate and acquired immune response against pulmonary *Mycobacterium bovis* bacille Calmette-Guerin infection. J Immunol, 2007, 178(6): 3786–3796. doi: 10.4049/jimmunol.178.6.3786.

[46] KHADER S A, BELL G K, PEARL J E, *et al*. IL-23 and IL-17 in the establishment of protective pulmonary $CD4^+$ T cell responses after vaccination and during *Mycobacterium tuberculosis* challenge. Nat Immunol, 2007, 8(4): 369–377. doi: 10.1038/ni1449.

[47] ZHENG X, ZHANG L, CHEN J, *et al*. Dendritic cells and Th17/Treg ratio play critical roles in pathogenic process of chronic obstructive pulmonary disease. Biomed Pharmacother, 2018, 108: 1141–1151. doi: 10.1016/j.biopha.2018.09.113.

[48] SONNENBERG G F, NAIR M G, KIRN T J, *et al*. Pathological versus protective functions of IL-22 in airway inflammation are regulated by IL-17A. J Exp Med, 2010, 207(6): 1293–1305. doi: 10.1084/jem.20092054.

[49] KREINDLER J L, BERTRAND C A, LEE R J, *et al*. Interleukin-17A induces bicarbonate secretion in normal human bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol, 2009, 296(2): L257–266. doi: 10.1152/ajplung.00344.2007.

[50] PEZZULO A A, TANG X X, HOEGGER M J, *et al*. Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. Nature, 2012, 487(7405): 109–113. doi: 10.1038/nature11130.

[51] RUTZ S, EIDENSCHENK C, OUYANG W. IL-22, not simply a Th17 cytokine. Immunol Rev, 2013, 252(1): 116–132. doi: 10.1111/imr.12027.

[52] KAWAI T, MATSUYAMA T, HOSOKAWA Y, *et al*. B and T lymphocytes are the primary sources of RANKL in the bone resorptive lesion of periodontal disease. Am J Pathol, 2006, 169(3): 987–998. doi: 10.2353/ajpath.2006.060180.

[53] ZHOU L, LE Y, TIAN J, *et al*. Cigarette smoke-induced RANKL expression enhances MMP-9 production by alveolar macrophages. Int J Chron Obstruct Pulmon Dis, 2019, 14: 81–91. doi: 10.2147/COPD.S190023.

[54] LOUHELAINEN N, RYTILÄ P, HAAHTELA T, *et al*. Persistence of oxidant and protease burden in the airways after smoking cessation. BMC Pulm Med, 2009, 9: 25. doi: 10.1186/1471-2466-9-25.

[55] CARAMORI G, ADCOCK I M, DI STEFANO A, *et al*. Cytokine inhibition in the treatment of COPD. Int J Chron Obstruct Pulmon Dis, 2014, 9: 397–412.

[56] DOMON H, TERAO Y. The role of neutrophils and neutrophil elastase in pneumococcal pneumonia. Front Cell Infect Microbiol, 2021, 11: 615959. doi: 10.3389/fcimb.2021.615959.

[57] EICKHOLZ P, ASENDORF A, SCHRÖDER M, *et al*. Effect of subgingival instrumentation on neutrophil elastase and C-reactive protein in Grade B and C periodontitis: exploratory analysis of a prospective cohort study. J Clin Med, 2022, 11(11): 3189. doi: 10.3390/jcm11113189.

[58] ARAL C A, ÖLÇER S N, ARAL K, *et al*. Oxidative stress, neutrophil elastase and IGFBP7 levels in patients with oropharyngeal cancer and chronic periodontitis. Oral Dis, 2020, 26(7): 1393–1401. doi: 10.1111/odi.13370.

[59] HIYOSHI T, DOMON H, MAEKAWA T, *et al*. Neutrophil elastase aggravates periodontitis by disrupting gingival epithelial barrier via cleaving cell adhesion molecules. Sci Rep, 2022, 12(1): 8159. doi: 10.1038/s41598-022-12358-3.

[60] JANOFF A, SLOAN B, WEINBAUM G, *et al*. Experimental emphysema induced with purified human neutrophil elastase: tissue localization of the

instilled protease. Am Rev Respir Dis, 1977, 115(3): 461–478.

[61] DAMIANO V V, TSANG A, KUCICH U, *et al*. Immunolocalization of elastase in human emphysematous lungs. J Clin Invest, 1986, 78(2): 482–493. doi: 10.1172/JCI112600.

[62] FUJITA J, NELSON N L, DAUGHTON D M, *et al*. Evaluation of elastase and antielastase balance in patients with chronic bronchitis and pulmonary emphysema. Am Rev Respir Dis, 1990, 142(1): 57–62. doi: 10.1164/ajrccm/142.1.57.

[63] OWEN C A. REVIEW Roles for proteinases in the pathogenesis of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis, 2008, 3(2): 253–268. doi: 10.1172/JCI60324.

[64] YILDIRIM E, KORMI I, BAŞOĞLU Ö K, *et al*. Periodontal health and serum, saliva matrix metalloproteinases in patients with mild chronic obstructive pulmonary disease. J Periodontal Res, 2013, 48(3): 269–275. doi: 10.1111/jre.12004.

[65] 王吉天, 刘志强, 张天翼, 等. 慢性阻塞性肺疾病频繁急性发作的牙周及唾液指标筛查的研究. 中华口腔医学杂志, 2019(6): 410–415. doi: 10.3760/cma.j.issn.1002-0098.2019.06.013.

[66] EBERSOLE J L, SCHUSTER J L, STEVENS J, *et al*. Patterns of salivary analytes provide diagnostic capacity for distinguishing chronic adult periodontitis from health. J Clin Immunol, 2013, 33(1): 271–279. doi: 10.1007/s10875-012-9771-3.

[67] CHURG A, ZHOU S, WRIGHT J L. Series "matrix metalloproteinases in lung health and disease": matrix metalloproteinases in COPD. Eur Respir J, 2012, 39(1): 197–209. doi: 10.1183/09031936.00121611.

[68] VERNOOY J H, LINDEMAN J H, JACOBS J A, *et al*. Increased activity of matrix metalloproteinase-8 and matrix metalloproteinase-9 in induced sputum from patients with COPD. Chest, 2004, 126(6): 1802–1810. doi: 10.1378/chest.126.6.1802.

[69] ILUMETS H, RYTILÄ P, DEMEDTS I, *et al*. Matrix metalloproteinases -8, -9 and -12 in smokers and patients with stage 0 COPD. Int J Chron Obstruct Pulmon Dis, 2007, 2(3): 369–379.

[70] JI J, Von SCHÉELE I, BERGSTRÖM J, *et al*. Compartment differences of inflammatory activity in chronic obstructive pulmonary disease. Respir Res, 2014, 15(1): 104. doi: 10.1186/s12931-014-0104-3.

[71] TRIPATHI P M, KANT S, YADAV R S, *et al*. Expression of toll-like receptor 2 and 4 in peripheral blood neutrophil cells from patients with chronic obstructive pulmonary disease. Oman Med J, 2017, 32(6): 477–485. doi: 10.5001/omj.2017.92.

[72] ZHOU X, HAN J, LIU Z, *et al*. Effects of periodontal treatment on lung function and exacerbation frequency in patients with chronic obstructive pulmonary disease and chronic periodontitis: a 2-year pilot randomized controlled trial. J Clin Periodontol, 2014, 41(6): 564–572. doi: 10.1111/jcpe.12247.

[73] KUCUKCOSKUN M, BASER U, OZTEKIN G, *et al*. Initial periodontal treatment for prevention of chronic obstructive pulmonary disease exacerbations. J Periodontol, 2013, 84(7): 863–870. doi: 10.1902/jop.2012.120399.

[74] SHEN T C, CHANG P Y, LIN C L, *et al*. Periodontal treatment reduces risk of adverse respiratory events in patients with chronic obstructive pulmonary disease: a propensity-matched cohort study. Medicine (Baltimore), 2016, 95(20): e3735. doi: 10.1097/MD.0000000000003735.

[75] CARDOSO E M, REIS C, MANZANARES-CÉSPEDES M C. Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. Postgrad Med, 2018, 130(1): 98–104. doi: 10.1080/00325481.2018.1396876.

[76] AGADO B E, CRAWFORD B, DELAROSA J, *et al*. Effects of periodontal instrumentation on quality of life and illness in patients with chronic obstructive pulmonary disease: a pilot study. J Dent Hyg, 2012, 86(3): 204–214.

[77] 钟南山. 慢性阻塞性肺病防治研究进展——呼吸系统疾病(1). 新医学, 1997(8): 439–440.

[78] LAMPRECHT B, SORIANO J B, STUDNICKA M, *et al*. Determinants of underdiagnosis of COPD in national and international surveys. Chest, 2015, 148(4): 971–985. doi: 10.1378/chest.14-2535.

[79] CASAS HERRERA A, MONTES De OCA M, LÓPEZ VARELA M V, *et al*. COPD underdiagnosis and misdiagnosis in a high-risk primary care population in four Latin American countries. A key to enhance disease diagnosis: the PUMA study. PLoS One, 2016, 11(4): e0152266. doi: 10.1371/journal.pone.0152266.

[80] LAUCHO-CONTRERAS M E, COHEN-TODD M. Early diagnosis of COPD: myth or a true perspective. Eur Respir Rev, 2020, 29(158): 200131. doi: 10.1183/16000617.0131-2020.

(2022 – 08 – 17收稿, 2022 – 12 – 22修回)

编辑 汤 洁