四川大学学报（医学版）　2025，56（5）：1281－1288
J Sichuan Univ（Med Sci）

在线全文

·论　著·

牙周炎通过促进肺部巨噬细胞M1极化加剧慢性阻塞性肺疾病进展*

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【摘要】 **目的**　研究巨噬细胞M1极化在介导牙周炎(periodontitis, PD)影响慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)进展中的重要作用。**方法**　收集伴牙周炎COPD患者肺泡灌洗液样本，基因表达分析M1极化相关基因的变化趋势；构建伴牙周炎COPD疾病动物模型，HE病理切片观察牙周炎对COPD进展的影响，通过流式细胞分析、免疫荧光观察及RT-qPCR检测分析牙周炎对COPD肺泡灌洗液及肺组织中巨噬细胞M1极化现象及相关基因表达的影响。**结果**　伴牙周炎COPD患者临床肺泡灌洗液样本中巨噬细胞M1极化相关基因*CD86*、诱生型一氧化氮合酶(inducible nitric oxide synthase, *iNOS*)、白介素(interleukin, *IL*)-*1β*、肿瘤坏死因子(tumor necrosis factor, *TNF*)-*α*、*IL-23*和*IL-6*表达较COPD组上调。疾病动物模型分析显示牙周炎影响COPD小鼠体重，伴牙周炎COPD组小鼠最终体质量〔(21.3±0.52) g，第34天〕低于COPD组〔(23.93±0.45) g，第34天〕，肺组织病理切片显示牙周炎能够促进COPD进展，伴牙周炎COPD小鼠肺泡扩张、肺泡壁断裂更明显。流式细胞分析显示伴牙周炎COPD组〔(31.36±2.51)%〕小鼠肺泡灌洗液中M1极化巨噬细胞较COPD组〔(23.19±1.07)%〕增多，荧光观察表明牙周炎也能促进COPD小鼠肺组织中巨噬细胞M1极化，基因表达分析伴牙周炎COPD组小鼠肺泡灌洗液及肺组织中巨噬细胞M1极化相关基因表达较COPD组均上调。**结论**　牙周炎能够促进肺部巨噬细胞M1极化加剧COPD疾病进展，加强口腔卫生管理及靶向抑制巨噬细胞M1极化可能是临床COPD防控的新方法。

【关键词】　慢性阻塞性肺疾病　牙周炎　M1极化　巨噬细胞

Periodontitis Aggravates Chronic Obstructive Pulmonary Disease Progression by Promoting Pulmonary Macrophage M1 Polarizations

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[Abstract]　**Objective**　To investigate the critical role of macrophage M1 polarization in mediating the effect of periodontitis on the progression of chronic obstructive pulmonary disease (COPD). **Methods**　Alveolar lavage fluid samples were collected from COPD patients with comorbid periodontitis, and gene expression analysis was performed to validate the changes in the expression of M1 polarization-related genes. A mouse model of COPD, with experimentally induced periodontitis, were established. Hematoxylin and eosin (HE) staining of pathological sections was performed to observe the effect of periodontitis on COPD progression. Flow cytometry, immunofluorescence staining, and reverse transcription quantitative polymerase chain reaction (RT-qPCR) were performed to analyze the effect of periodontitis on macrophage M1 polarization and the expression of relevant genes in the alveolar lavage fluid and lung tissues. **Results**　In clinical samples of alveolar lavage fluid from COPD patients with periodontitis, the expression of macrophage M1 polarization-related genes, including *CD86*, inducible nitric oxide synthase (*iNOS*), interleukin (*IL*)-*1β*, tumor necrosis factor (*TNF*)-*α*, *IL-23*, and *IL-6*, was upregulated compared with that of COPD patients without periodontitis. Analysis of a mouse disease model revealed that periodontitis affected the growth of COPD mice, with the final body mass of mice in the periodontitis and COPD comorbid group ([21.3 ± 0.52] g, day 34) lower than that of the COPD group ([23.93 ± 0.45]

* 四川省自然科学基金(No. 2024NSFSC0739)资助

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出版日期：2025-09-20

g, day 34). Pathological sections of the lung tissue showed that periodontitis exacerbated COPD progression, with more pronounced alveolar expansion and alveolar wall destruction observed in the periodontitis and COPD comorbid group. Flow cytometry revealed a higher proportion of M1-polarized macrophages in alveolar lavage fluid from COPD and periodontitis comorbid mice ([31.36 ± 2.51]%) compared with the COPD mice ([23.19 ± 1.07]%). Immunofluorescence assays indicated that periodontitis also promoted macrophage M1 polarization in the lung tissue of COPD mice. Gene expression analysis demonstrated that M1 polarization-related gene expression was significantly upregulated in both the alveolar lavage fluid and lung tissue of mice in the COPD and periodontitis co-morbid group compared to the COPD group. **Conclusion** Periodontitis exacerbates COPD progression by promoting macrophage M1 polarization in the lungs. Enhancing oral hygiene management and targeting the inhibition of macrophage M1 polarization may represent new therapeutic strategies for the clinical prevention and control of COPD.

[Key words] Chronic obstructive pulmonary disease Periodontitis M1 polarization Macrophages

慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)是一种持续性以气流阻塞、肺功能恶化、咳嗽带痰和呼吸短促为特征的慢性全身性炎症性疾病[1-2]。约90%死亡病例集中在亚洲和非洲,是全球第三大死亡原因[3-5]。全球COPD发病率已达10.3%[6],中国更是高达13.7%[7]。除吸烟外,二手烟、职业暴露、空气污染物和既往肺部感染史(包括肺部结核感染)等也是COPD的重要危险因素[8-9]。

牙周炎(periodontitis, PD)作为牙周组织的慢性感染性疾病[10],与COPD存在显著正相关[11-14]。研究表明,牙周炎患者COPD发病风险及严重程度更高[13]。且牙周炎相关指标与肺功能指标呈负相关[15]。但具体机制仍有待进一步阐明。

巨噬细胞M1极化〔分泌白介素(interleukin, IL)-6、肿瘤坏死因子(tumor necrosis factor, TNF)-α等促炎因子〕在COPD发病中起关键作用[16-18],但其在牙周炎影响COPD进程中的作用尚不清楚。因此,本研究拟通过研究临床样本和动物模型,探讨牙周炎对COPD的促进作用及对肺部巨噬细胞M1极化的调控作用,为COPD防治提供新的思路。

1 资料与方法

1.1 临床样本收集

本研究经四川大学华西口腔医院医学伦理委员会的批准(批准号WCHSIRB-D-2022-473),临床样本收集前所有患者详细了解本研究相关内容并签署知情同意书。于四川大学华西医院支气管镜检中心收集呼吸科临床确诊的COPD患者肺泡灌洗液样本。本研究共收集肺泡灌洗液样本40例,其中COPD 21例,伴牙周炎COPD 19例(PCR检测标本中牙龈卟啉单胞菌阳性)。样本收集后离心取沉淀,采用RNA提取试剂盒(MolPure® Cell/Tissue Total RNA Kit)根据说明书进行RNA提取、gDNA去除、逆转录,所得cDNA通过定量实时聚合酶链式反应试剂盒〔SYBR Green Master Mix (No Rox)〕进行RT-qPCR扩增反应,采用$2^{-\Delta\Delta C_T}$法分析各样本中M1极化相关基因表达情况,基因引物序列见表1,以*GAPDH*作为内参基因。

表1 临床患者样本各基因引物列表

Table 1 Primer sequences of target genes used for clinical patient samples

Primers	Sequences (5'–3')
GAPDH-F	ACAACTTTGGTATCGTGGAAGG
GAPDH-R	GCCATCACGCCACAGTTTC
CD86-F	CTGCTCATCTATACACGGTTACC
CD86-R	GGAAACGTCGTACAGTTCTGTG
iNOS -F	TTCAGTATCACAACCTCAGCAAG
iNOS -R	TGGACCTGCAAGTTAAAATCCC
IL-1β-F	ATGATGGCTTATTACAGTGGCAA
IL-1β-R	GTCGGAGATTCGTAGCTGGA
IL-23-F	CTCAGGGACAACAGTCAGTTC
IL-23-R	ACAGGGCTATCAGGGAGCA
IL-6-F	ACTCACCTCTTCAGAACGAATTG
IL-6-R	CCATCTTTGGAAGGTTCAGGTTG
TNF-α-F	GAAAACAACCCTCAGACGCC
TNF-α-R	CGATCACTCCAAAGTGCAGC

iNOS: inducible nitric oxide synthase; *IL-1β*: interleukin 1β; *IL-23*: interleukin 23; *IL-6*: interleukin 6; *TNF-α*: tumor necrosis factor α.

1.2 动物模型构建

本研究经四川大学华西口腔医学院伦理委员会批准(WCHSIRB-D-2022-624),实验小鼠购自成都达硕实验动物有限公司,选用9只7周龄SPF雄性C57BL/6J小鼠,分为健康对照组、COPD组和COPD+PD组,每组3只小鼠。所有小鼠用含四联抗生素的饮用水处理2 d后, COPD+PD

组小鼠开始构建牙周炎模型：1.25%阿佛丁(0.2 mL/10 g)对小鼠进行麻醉后，采用5-0无菌缝合丝线牙周接扎+隔天口内牙龈卟啉单胞菌接菌感染的方式进行牙周炎模型构建[19]。构建牙周炎模型4 d后，COPD组和COPD+PD组的小鼠开始构建COPD模型：采用猪胰腺弹性蛋白酶(porcine pancreas elastase, PPE)两次气管内给药(2.5个单位/次)+烟雾发射TSE装置(TSE Systems, 中国)将小鼠连续4周每天持续暴露于香烟烟雾中2 h[19]。健康对照组小鼠不做处理。隔天对小鼠进行生长监测并记录体质量。第34天，在麻醉状态(1.25%三溴乙醇，0.2 mL/10 g)下通过颈椎脱臼法处死小鼠。

1.3　HE染色

取肺组织样本经4%多聚甲醛固定、流水洗涤后、梯度酒精脱水、二甲苯透明化、石蜡包埋后，切片机切片(5 μm/张)。采用HE染色试剂盒(碧云天，中国)，切片经脱蜡至水、苏木素染色、伊红染色、脱水封片后，于倒置显微镜下(莱卡，德国)下进行各组小鼠肺组织形态观察。

1.4　流式细胞术分析

取肺泡灌洗液经离心、流式缓冲液重悬得到单细胞悬液，4 ℃离心(350×*g*, 5 min)收集细胞沉淀，进行流式上机样本制备：依次经死活染色(Fixable Viability Kit, BioLegendCat# L423105)，封闭(TruStain FcX, BioLegend Cat# 101320)，抗体染色〔CD45(BioLegend Cat# 103140)、F4/80(BioLegend Cat# 123130)、CD86(BioLegend Cat#105008)〕，固定后，洗去多余抗体，流式缓冲液重悬细胞，流式细胞仪Cytoflex(Beckman, 德国)上机检测，采用Cytexpert软件进行分析。

1.5　免疫荧光分析

肺组织石蜡切片经烤片、二甲苯脱蜡、抗原修复(热修复)、打孔、内源性过氧化物酶阻断、山羊血清封闭后，将CD86 Polyclonal Antibody(1∶200稀释)滴加样本上，4 ℃冰箱过夜孵育，PBS清洗后，将荧光二抗CoraLite 488-conjugated Goat Anti-Rabbit IgG H&L(1∶500稀释)滴加在样本上，室温暗室中孵育1 h。PBS清洗后，DAPI染细胞核约10 min，PBS清洗，然后用荧光防淬灭剂封片。荧光倒置显微镜镜下(莱卡，德国)观察、采图，比较各组小鼠肺组织中M1极化情况。

1.6　实时荧光定量PCR分析基因表达

将肺泡灌洗液样本离心后收集沉淀，小鼠肺组织样本称重后研磨收集研磨匀浆，根据1.1中试剂盒及方法进行RNA提取、gDNA去除、逆转录反应得到cDNA样本并进行RT-qPCR扩增反应，采用$2^{-\Delta\Delta C_T}$法分析各组小鼠肺泡灌洗液样本及肺组织样本中M1极化相关基因表达情况，基因引物序列见表2，以*GAPDH*作为内参基因。

表 2　小鼠样本各基因引物列表

Table 2　Primer sequences of target genes used for mouse samples

Primers	Sequences (5’–3’)
GAPDH-F	AGGTTGTCTCCTGCGACTTCA
GAPDH-R	CCAGGAAATGAGCTTGACAAA
CD86-F	TGTTTCCGTGGAGACGCAAG
CD86-R	TTGAGCCTTTGTAAATGGGCA
iNOS -F	GTTCTCAGCCCAACAATACAAGA
iNOS -R	GTGGACGGGTCGATGTCAC
IL-1β-F	CAACCAACAAGTGATATTCTCCATG
IL-1β-R	ATCCACACTCTCCAGCTGCA
IL-23-F	ATGCTGGATTGCAGAGCAGTA
IL-23-R	ACGGGGCACATTATTTTTAGTCT
IL-6-F	GAGGATACCACTCCCAACAGACC
IL-6-R	AAGTGCATCATCGTTGTTCATACA
TNF-α-F	GACGTGGAACTGGCAGAAGAG
TNF-α-R	TTGGTGGTTTGTGAGTGTGAG

The abbreviations are explained in the note to Table 1.

1.7　统计学方法

使用GraphPad Prism(Version 9)进行统计分析及作图。所得数据使用Levene's检验进行方差齐性分析后，两组之间NOVA比较采用*t*检验或者Kruskal-Wallis *H*检验进行统计学差异分析，多组间比较时，采用单因素方差分析，并在满足条件时进行Tukey's事后多重比较。$P<0.05$为差异有统计学意义。

2　结果

2.1　伴牙周炎COPD患者肺泡灌洗液样本中M1极化相关基因表达上调

相较于COPD组，COPD+PD组样本中M1极化相关基因*CD86*、*iNOS*、*IL-1β*、*TNF-α*、*IL-23*和*IL-6*表达上调(图1)，提示牙周炎能够促进COPD患者肺泡灌洗液中巨噬细胞的M1极化。

2.2　牙周炎影响COPD小鼠生长

实验中各组小鼠体质量变化曲线如图2所示。COPD组小鼠体质量自建模开始〔第6天，(23.87±0.35) g〕逐渐下降，至第12天时达到谷底(20.77±0.91) g，后逐渐恢复，第34天时体质量为(23.93±0.45) g，从第8天开始，COPD组小鼠体质量明显低于Control组($P<0.05$)。COPD+PD组小

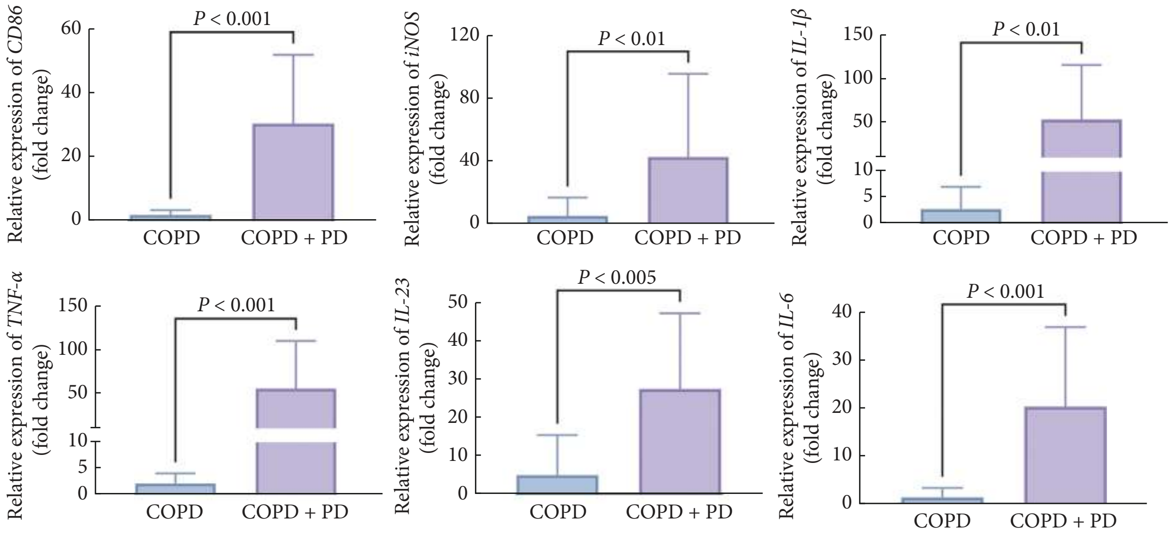

图 1 COPD患者（n=21）及伴牙周炎COPD患者（n=19）肺泡灌洗液中M1极化相关基因的表达

Fig 1 Expression of M1 polarization-related genes in bronchoalveolar lavage fluid from COPD patients (n = 21) and patients with COPD and periodontitis (n = 19)

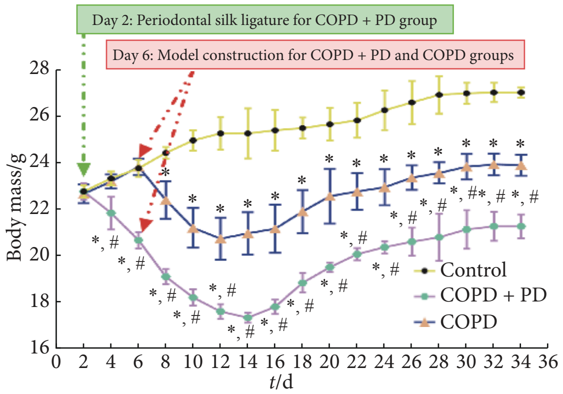

图 2 各组小鼠体质量变化曲线（n=3）

Fig 2 Body mass changes of mice in different groups (n = 3)

* P < 0.05, vs. control group; $^\#$ P < 0.05, vs. COPD group.

鼠建模后体质量明显下降，由(22.8±0.36) g(第2天)降至(20.7±0.36) g(第6天)，构建COPD模型后，小鼠体质量继续降至(17.37±0.21) g(第14天)，再最终恢复至(21.3±0.52)g(第34天)，在此期间(第4天～第34天)COPD+PD组体质量明显低于另两组(P<0.05)。

2.3 牙周炎促进COPD进展

小鼠肺组织病理切片HE染色结果显示，健康对照组肺组织结构完整，肺泡大小均匀，肺组织健康(图3A)，COPD组肺组织明显病损，肺泡扩大，肺泡壁扩张断裂(图3B)，COPD+PD肺组织病变程度较COPD组明显加重，肺组织可见大面积肺泡腔融合形成蜂窝样结构，肺泡扩大、肺泡壁大范围断裂消失(图3C)。

2.4 牙周炎促进COPD小鼠肺泡灌洗液中巨噬细胞M1极化

动物模型小鼠肺泡灌洗液样本的流式结果显示，对照组肺泡灌洗液中M1极化现象较少，COPD组和COPD+PD组M1极化增加，其中，相较于COPD组，COPD+PD组M1极化进一步增加(图4)。肺泡灌洗液样本基因表达分析的结果显示，M1极化因子*iNOS*、*CD86*以及促炎因子*IL-1β*、*TNF-α*和*IL-23*在3组中呈连续递增趋势，COPD+PD组表达水平最高，且组间差异均有统计学意义，*IL-6*在COPD组和COPD+PD组均较对照组显著升高，但两组间差异无统计学意义(图5)。

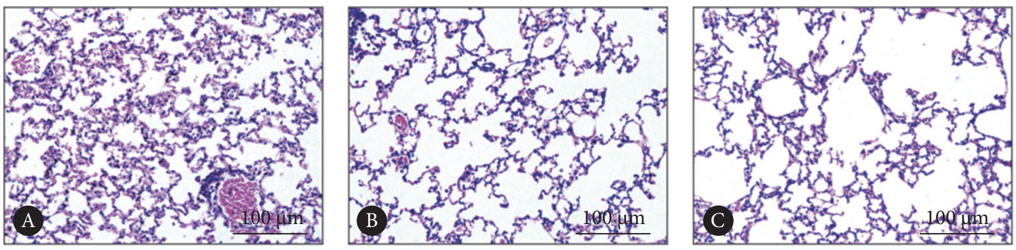

图 3 小鼠肺组织HE染色结果

Fig 3 HE-stained lung tissue samples of mice

A, Control group; B, COPD group; C, COPD + PD group.

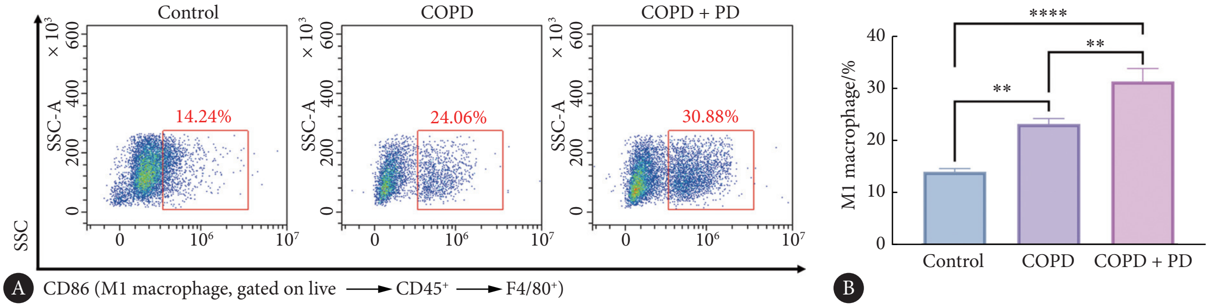

图 4 小鼠肺泡灌洗液中M1极化情况

Fig 4 M1 polarization of macrophages in bronchoalveolar lavage fluid from mice

A, Representative flow cytometry plots of bronchoalveolar lavage fluid from mice in different groups; B, quantitative analysis of M1-polarized macrophages in bronchoalveolar lavage fluid from mice. ** $P < 0.01$; **** $P < 0.001$. $n = 3$.

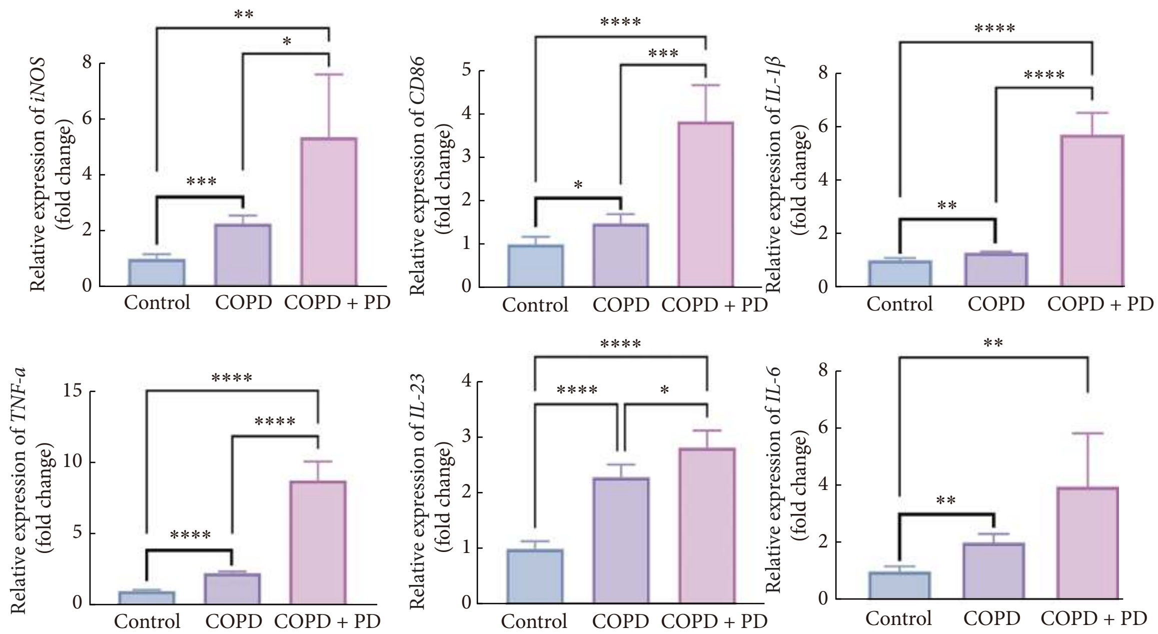

图 5 小鼠肺泡灌洗液中M1极化相关基因的表达

Fig 5 Expression of M1 polarization-related genes in bronchoalveolar lavage fluid from mice

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$; **** $P < 0.001$. $n = 3$.

2.5 牙周炎促进COPD小鼠肺组织中巨噬细胞M1极化

肺组织切片免疫荧光染色结果显示，相较于COPD组，COPD+PD组肺组织切片中M1极化即CD86⁺荧光明显增强（图6），同时，肺组织基因表达结果显示，牙周炎能够促进COPD小鼠肺组织中M1极化相关基因*iNOS*、*CD86*、*IL-1β*、*TNF-α*、*IL-23*、*IL-6*的表达上调（图7）。

3 讨论

牙周炎是以牙菌斑生物膜为主要致病因素的牙周组织的慢性炎症性疾病，被认为是多种系统性疾病（包括COPD、心血管系统疾病、糖尿病、高血压、各种肿瘤等）的潜在危险因素[20-22]。众所周知，慢性呼吸系统疾病是全球主要的发病率和死亡率高的疾病，其中COPD引起的死亡最多，被认为是全球第三大致死性疾病[23]。

牙周炎和COPD是常见的两种慢性炎症性疾病，已有的临床队列研究和Meta分析报道了牙周炎和COPD之间存在正相关性[11, 24]。牙周状况越差，COPD症状越严重，牙周菌斑指数与COPD严重程度之间存在相关性[25]，牙周炎可能是COPD的一个重要预测因子[26-27]，牙周相关情况如牙龈指数（gingiva index, GI）、探诊出血（bleeding on probing, BOP）、探诊深度（probing depth, PD）、临床附着丧失（clinical attachment loss, CAL）与肺功能指数FEV1/FVC（第一秒用力呼气容积与用力肺活量之比，ratio of forced expiratory volume in one second to forced vital capacity）及FEV1值呈负相关，提示牙周健康状况不佳与慢性阻塞性肺疾病进展相关[15, 28]。对900名无COPD

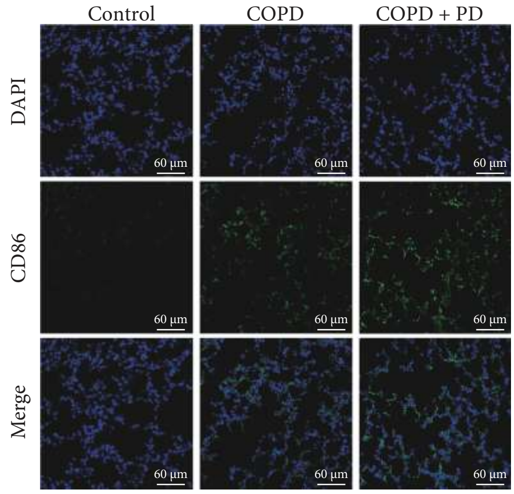

图 6 牙周炎促进COPD小鼠肺组织中巨噬细胞M1极化

Fig 6 Periodontitis promotes M1 polarization of macrophages in the lung tissues of COPD mice

的社区居民进行了5年的长时间随访观察结果显示,重度牙周炎组患者发展COPD的危险性更高,与牙周健康人群和轻中度牙周炎患者群体相比,COPD的相对危险度为3.51[13]。伴牙周炎的COPD患者其肺功能减弱及加重频率会比牙周健康的COPD患者更严重,通过进行牙周基础治疗及口腔健康维护,COPD患者的肺功能减弱及疾病急性加重频率可以得到很好的控制[29],这些研究提示牙周炎在一定程度上加重了COPD患者的肺部不适。我们通过构建伴牙周炎COPD小鼠疾病模型发现,与临床队列相关报道一致,在小鼠模型中,牙周炎能够促进COPD进展,COPD+PD组小鼠疾病严重程度进一步增加,肺组织病损进一步加重,肺泡扩大、肺泡壁扩展断裂最严重。

巨噬细胞能够极化为不同表型进而影响肺部疾病的转归[30-32],在健康肺部,大多数的巨噬细胞通常呈非极化状态,在COPD患者肺部,巨噬细胞数量明显增多,巨噬细胞极化现象明显加重[33]。大量研究结果表明M1极化现象介导的炎症反应在COPD疾病病理中发挥了重要的作用,LEE等[16]通过文献回顾得出,M1相关标志物(iNOS)和细胞因子(IL-1β、IL-6、IL-8、TNF-α)在COPD患者中升高,提示M1极化在COPD中的致病作用。红景天苷通过抑制JNK/c-Jun通路减轻了香烟烟雾暴露诱导的肺泡巨噬细胞的M1极化从而减轻COPD的肺部炎症[34]。吸入性皮质类固醇通过抑制肺巨噬细胞M1极化、促进M2极化在COPD的治疗中具有重要意义[35]。同样,SUN等[17]的数据表明麦角甾醇通过降低M1极化和增加M2极化来发挥治疗COPD的作用。这些结果表明M1极化在COPD的病理中扮演了重要的致病角色。

同时,已有研究显示牙周炎能够通过影响巨噬细胞的极化从而影响多种系统疾病的进展。有学者通过动物模型研究发现口内接种感染牙龈卟啉单胞菌能够促进肠道巨噬细胞M1极化并进一步促进肠道炎症进展[36]。LYU等[37]指出,人β-防御素3可以通过促进巨噬细胞M2极化、减少M1极化来治疗牙周炎相关的全身性炎症反应,提示M1极化在介导牙周炎引起系统性炎症反应中可能发挥了重要作用。然而M1极化在伴牙周炎COPD进展中的作用尚不清楚,牙周炎能否通过促进肺部巨噬细胞M1极化从而加重COPD的进展仍需要进一步的探索。我

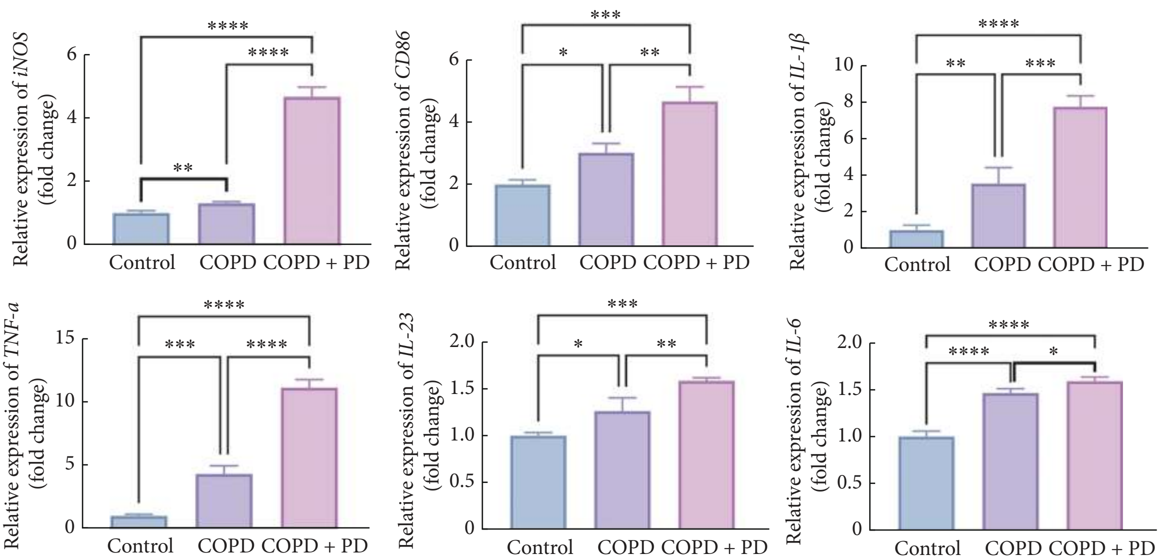

图 7 牙周炎促进COPD小鼠肺组织中M1极化相关基因的表达

Fig 7 Periodontitis promotes the expression of M1 polarization-related genes in the lung tissues of COPD mice

* P < 0.05; ** P < 0.01; *** P < 0.005; **** P < 0.001. n = 3.

们的研究结果发现在伴牙周炎COPD患者的临床肺泡灌洗液样本中巨噬细胞M1极化相关的基因表达较不伴牙周炎COPD患者中上调，提示巨噬细胞M1极化可能是COPD的重要病理机制之一，同时也是牙周炎促进COPD进展的重要途径之一。进一步构建伴牙周炎COPD的小鼠疾病模型对该现象进行验证，显示巨噬细胞M1极化在COPD中发挥了重要的病理作用。相较于健康对照组，COPD组、COPD+PD组小鼠肺部M1极化巨噬细胞比例增加，M1极化相关基因表达上调。并且，牙周炎能够通过促进COPD小鼠肺部巨噬细胞M1极化加剧COPD的疾病进展，相较于COPD组，COPD+PD组小鼠疾病程度加重，肺部M1极化巨噬细胞增多，基因表达进一步上调。本研究仍存在一定的局限性，研究过程中涉及多指标的组间比较，可能存在多重假设检验带来的Ⅰ型错误风险，因此本研究结果仅作为探索性分析，需在更大样本及进一步实验中加以验证。

本研究发现伴牙周炎COPD患者肺泡灌洗液中巨噬细胞M1极化相关基因的表达上调，提示M1极化巨噬细胞可能在COPD病理以及牙周炎促进COPD进展的过程中发挥了重要作用，进一步构建动物模型我们观察到牙周炎可以加剧COPD的进展，并发现巨噬细胞M1极化相关免疫机制在牙周炎促进COPD的介导中发挥重要作用。牙周炎的存在加剧了COPD小鼠肺部M1巨噬细胞的活化，导致COPD严重程度加重。因此，牙周健康维护和靶向抑制巨噬细胞M1极化可能是COPD尤其是伴牙周炎COPD临床防控的一种新策略。

* * *

作者贡献声明 李静负责数据审编、正式分析、研究方法和初稿写作，熊开新和汤博钰负责调查研究和提供资源，夏子怡和唐昭负责可视化，李燕负责论文构思、经费获取、研究方法和审读与编辑写作。所有作者已经同意将文章提交给本刊，且对将要发表的版本进行最终定稿，并同意对工作的所有方面负责。

Author Contribution LI Jing is responsible for data curation, formal analysis, methodology, and writing--original draft. XIONG Kaixin and TANG Boyu are responsible for investigation and resources. XIA Ziyi and TANG Zhao are responsible for visualization. LI Yan is responsible for conceptualization, funding acquisition, methodology, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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Declaration of Conflicting Interests All authors declare no competing interests.

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(2025 – 01 – 20收稿, 2025 – 09 – 02修回)

编辑 汤 洁