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呼吸道微生物组与呼吸道感染

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摘要 近年来, 呼吸道微生物组在呼吸道感染中的作用备受关注. 呼吸道微生物组对呼吸生理、免疫调控及多种呼吸道疾病的发生和发展具有重要影响. 呼吸道不同部位如鼻腔、鼻咽、口咽和下呼吸道的微生物组成也不同. 正常情况下, 呼吸道中的共生菌通过占据生态位、促进定植抗性来维持稳态. 但当这种稳态平衡被打破时, 就会发生呼吸道菌群失调, 增加感染风险. 二代测序技术的进步促进了呼吸道微生物组的高精度解析, 越来越多的研究揭示了菌群失调与呼吸道感染的复杂关系. 呼吸道感染会导致微生物多样性下降和菌群结构发生变化, 不同类型的感染对呼吸道微生物组的影响也不同. 呼吸道菌群失调不仅加重了炎症反应, 还可能引发慢性气道病变和组织损伤. 呼吸道微生物组不仅可以作为呼吸感染的诊断和预后标识物, 还可以作为潜在干预手段预防呼吸道感染. 本文综述了呼吸道感染过程中呼吸道微生物组的变化规律及其与宿主的互作机制. 未来研究应进一步探索微生物组与宿主免疫的互作机制, 开发新的诊断和治疗策略, 提升当前的呼吸道感染临床救治水平.

关键词 呼吸道微生物组, 呼吸道感染, 菌群失调, 免疫互作

人类的历史也是人类与微生物共生演化的历史. 呼吸道是人类与外界环境接触最大面积的器官之一, 呼吸道表面积高达100 m^2, 微生物几乎存在于呼吸道所有部位. 呼吸道微生物组参与到呼吸生理的成熟和局部免疫调控, 与多种呼吸道疾病的发生和进展密切相关.

人体呼吸道在解剖学上分为上、下呼吸道, 上呼吸道包括鼻腔、鼻窦、咽喉和声门上部, 下呼吸道包括气管、支气管和肺部, 不同解剖部位的微生物组成不同. 当菌群结构偏离正常状态时, 就会发生菌群失调, 表现为益生菌和共生菌丰度下降和潜在致病菌丰度上升. 近十年来, 基于非培养方法的二代测序技术极大地促进了呼吸道微生物组的研究进展, 研究发现, 菌群失调与多种呼吸疾病的发生发展密切相关, 特别是在慢性阻塞性肺病和支气管扩张症等慢性气道疾病中发现多种菌群相关的急性加重机制. 然而在急性呼吸道感染中, 由于通常存在致病微生物, 传统的研究大多聚焦于典型呼吸道病原致病机制, 呼吸道菌群在下呼吸道感染特别是肺炎发生发展中的作用常常被忽视. 近年来, 呼吸道感染越来越受到重视, 呼吸道微生物组在呼吸道感染中的研究取得了突出进展. 本文综述了近年来呼吸道微生物组在呼吸道感染中变化规律及其与疾病临床特征的关系, 为今后本领域的进一步研究提供参考和启示.

1 呼吸道微生物组的主要分布

成年人的呼吸道沿着鼻腔、鼻咽、口咽、气管和

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肺部, 形成明显生理和微生物梯度. 从上呼吸道到肺部, 气道中的酸碱度pH逐渐升高, 氧分压逐渐降低, 二氧化碳分压升高[1,2]. 相对湿度(relative humidity, RH)和温度的增加主要发生在鼻腔, 随后沿着下气道轻微增加[3,4]. 这种生理梯度的改变, 也塑造了呼吸道微生物在不同的呼吸区间形成不同的菌群结构. 鼻腔的主要微生物包括葡萄球菌属(*Staphylococcus*)、丙酸杆菌属(*Propionibacterium*)、棒状杆菌属(*Corynebacterium*)、莫拉菌属(*Moraxella*)和链球菌属(*Streptococcus*). 鼻咽区域菌群与鼻腔类似, 莫拉菌属、葡萄球菌属、棒状杆菌属和链球菌属等微生物依然占据主导地位, 其他主要微生物还包括多形杆菌属(*Dolosigranulum*)、嗜血杆菌属(*Haemophilus*)等. 口咽部微生物与鼻腔和鼻咽部差异较大, 主要菌群中除了链球菌属外, 还包括普雷沃菌属(*Prevotella*)、韦荣氏球菌属(*Veillonella*)、罗氏属(*Rothia*)、纤毛菌属(*Leptotrichia*)、奈瑟菌属(*Neisseria*)和梭杆菌属(*Fusobacterium*)[3,5](图1). 相比较于口腔, 鼻腔和皮肤的微生物之间存在更强烈的联系[6].

下呼吸道的微生物组相对简单, 载量较低, 主要由口腔共生菌组成, 如链球菌属、韦荣氏球菌属和普雷沃氏菌属. 口咽的微生物群可以通过微吸入或其他方式进入下呼吸道, 影响呼吸健康. 口腔微生物向肺部的传播具有异质性, 在肺部的富集与肺功能下降和肺部促炎细胞因子增加相关[7]. 同时, 肺部菌群的组成受呼吸道清除机制(如咳嗽、黏液纤毛运输和先天免疫系统)的严格控制, 以防止病原体的定植和感染.

上呼吸道由于与环境密切接触, 微生物在不同个体间差异化程度较高, 但鼻腔微生物变化程度高于口咽, 表现出更多的个体化特征[8].

2 呼吸道微生物组在呼吸道感染中的作用

2.1 呼吸道病毒感染与呼吸道微生物组

2.1.1 新型冠状病毒感染(COVID-19)

2019冠状病毒病(corona virus diesease 2019, COVID-19)的严重程度与呼吸道微生物组密切相关. 随着COVID-19严重程度增加, 患者口咽部α多样性往往会下降[9~11], 口咽部微生物的组成和动态变化与COVID-19的死亡率显著相关. 在严重的COVID-19患者中, 嗜血杆菌和奈瑟菌的相对丰度减少, 且在不同的研究中呈现一致性[12~14]. 韦荣球菌, 特别是小韦荣球菌(*Veillonella parvula*)可能COVID-19患者的潜在生物标志物之一[15]. 此外, 入院时链球菌丰度越高, 预后越好[16].

鼻咽部微生物组与COVID-19患者的严重程度和临床结局之间的关联性研究结果缺乏一致性. Babenko等人[17]和Feehan等人[18]的研究分别发现, 罗氏菌和链球菌与更严重的疾病状态和肺部损伤程度升高相关. 但在另一个研究中[19], 重症COVID-19患者鼻咽部的机会性病原体(包括上述的细菌种属)的相对丰度较轻症患者更低. 不同研究结果之间缺乏一致性可能是因为

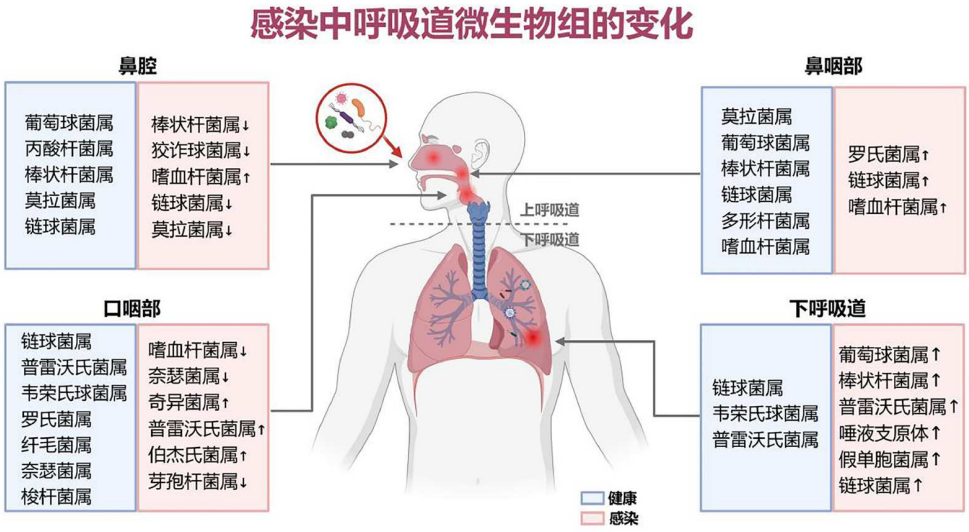

图 1 人体呼吸道微生物组的分布(由BioRender制作)
Figure 1 Distribution of the human respiratory microbiome, created with BioRender

存在混杂因素，或鼻咽部微生物组与这些特征的关联性本身比较弱.

与健康人和轻症患者相比，重症COVID-19患者的肺部更有可能出现α多样性降低和细菌载量增加的情况. 具体来说，插管的COVID-19患者下呼吸道微生物主要以葡萄球菌等病原微生物为主，并呈现高度的动态变化特征[13]. 此外, 这些患者肺部细菌和真菌负荷增加与拔管成功率降低之间存在显著关联[20].

2.1.2 流感病毒感染

呼吸道微生物组的变化可能会影响流感的易感性[21], 且这种易感性与年龄存在一定关联[22]. 在小鼠模型中, 流感病毒(influenza A virus, IAV)感染后, 细菌入侵阈值降低，主要是由于呼吸道内细菌组成的变化所引起, 而与总体细菌丰度的变化关系不大, 其中共生菌如婴儿链球菌(*Streptococcus infantis*)和无乳链球菌(*Streptococcus mitis*), 可能在抵抗这些病原菌的过度生长方面起到关键作用[23].

丁涛等人[24]发现, 不同亚型IAV引起的急性呼吸道感染在口咽微生物组成上存在差异. 在甲型流感患者中，主要物种是奇异菌属(*Atopobium*)和普雷沃氏菌属, 而在乙型流感患者中，伯杰氏菌属(*Bergeyella*)和普雷沃氏菌占主要地位[23]. 此外，在甲型H3N2或乙型流感的队列中也发现，疫苗接种也与微生物群落组成相关, 这可能意味着接种流感疫苗不仅可以预防流感感染, 还可能在控制继发细菌感染方面发挥作用[24].

2.1.3 其他呼吸道病毒感染

人腺病毒(*human adenovirus*, HAdV)是儿童呼吸道感染的重要病原体，占儿童社区获得性肺炎病例的4%~10%[25]. 腺病毒感染常伴有支原体混合感染[26]. 研究表明, HAdV感染的儿童其肺部微生物多样性高于肺炎支原体(*M. pneumoniae*)感染患者. 与单纯肺炎支原体感染的患者相比，合并HAdV感染的患者BALF微生物丰富度下降，但β多样性升高[27]. 其原因可能在于，肺炎支原体通过直接竞争或激活细菌清除机制来抑制其他细菌生长，但HAdV感染则会损害肺部上皮细胞，并抑制免疫反应, 从而促进细菌生长[28,29].

呼吸道合胞病毒(*respiratory syncytial virus*, RSV)感染与鼻咽微生物密切相关，主要表现为流感嗜血杆菌(*Haemophilus influenzae*)和肺炎链球菌(*Streptococcus pneumoniae*)的增多[30]. 此外, RSV与这两种细菌之间似乎存在双向互作. Kanmani等人[31]发现，通过将健康人上呼吸道微生物的组成成分之一的假白喉棒状杆菌(*Corynebacterium pseudodiphtheriticum*)滴注到幼年小鼠的鼻腔内，可以增强小鼠对RSV和肺炎球菌继发感染的抵抗力. 呼吸道共生菌可以作为增强病毒防御的有效手段.

鼻病毒(*rhinovirus*，RV)感染与呼吸道微生物组变化也具有相关性[32,33]. 随着RV载量增加，棒状杆菌和狡诈球菌属(*Dolosigranulum*)丰度减少，而嗜血杆菌的丰度则增加. 此外，链球菌和莫拉菌丰度也随着RV复制水平的变化而同时增减. 棒状杆菌和狡诈球菌属的富集可能有助于感染者在鼻病毒感染期间维持正常的呼吸道生理功能, 从而减轻或预防呼吸道症状[34].

2.2 呼吸道细菌感染与呼吸道微生物组

细菌性肺炎会破坏肺部微生物的稳态，通常导致微生物载量升高和多样性减少[35], 炎症反应加剧, 致病菌丰度增加[36]. 反之，α多样性的增加也可以作为重症肺炎患者临床康复的生物标志物[37]，病原体的生物量也与患者临床转归密切相关[38]. 在感染过程中, 呼吸道优势物种可能会被包括真菌在内的机会性病原体所取代, 导致继发感染. 除典型病原体外, 通常被认为无致病性的共生微生物在某些场景下也会引发细菌性肺炎[39].

2.2.1 肺炎链球菌

肺炎链球菌是社区获得性肺炎(community-acquired pneumonia, CAP)最常见的病原体之一[40], 其正常定植不会导致上呼吸道菌群发生重大变化[41]，只有少部分携带者会发展成肺炎[42]. 小鼠感染肺炎链球菌后，除肠杆菌科(*Enterobacteriaceae*)细菌外，其他细菌的相对丰度总体下降[41]. 肺炎链球菌、流感嗜血杆菌和卡他莫拉菌(*Moraxella catarrhalis*)等常见致病菌可增强彼此的致病性[43,44]. 在混合生物膜中, 肺炎链球菌可增强卡他莫拉菌对大环内酯类药物的耐药性，而卡他莫拉菌可保护肺炎链球菌不受β-内酰胺类药物的影响[45]. 流感嗜血杆菌还能通过群体感应(quorum sensing)保护卡他莫拉菌免受抗生素的影响[46]. 虽然呼吸道致病菌之间的互作可促进感染，但呼吸道共生菌对肺炎链球菌感染具有抵抗作用. 单次吸入口腔共生菌后, 虽然共生菌在下呼吸道中会被迅速清除, 但会诱导延长的Th17反应，继而降低宿主对肺炎链球菌的易感性[47]. 此外，黑色普雷沃菌(*Prevotella melaninogenica*)可以抑制肺炎链球菌对小鼠的感染，促使病原体迅速从肺部清除, 在小鼠共感染模型中提高存活率. 这一反

应主要通过激活Toll样受体(Toll-like receptors-2, TLR2)、调节白介素10(interleukin10, IL-10)和招募中性粒细胞触发宿主先天性免疫, 从而抵御肺炎链球菌的侵袭[48].

2.2.2 铜绿假单胞菌

铜绿假单胞菌(*Pseudomonas aeruginosa*)是医院获得性肺炎(hospital-acquired pneumonia, HAP)的主要病原体之一. 既往抗生素治疗是肺部铜绿假单胞菌感染的独立危险因素, 研究表明, 这是因为广谱抗生素耗竭了微生物群, 降低IgA水平, 使得小鼠抵抗力受损, 增加对铜绿假单胞菌的易感性. 在小鼠模型中, 为了评估肠道产碳青霉烯酶肠杆菌(carbapenemase-producing *Enterobacterales*, CPE)定植对宿主抵抗肺部感染的影响, 通过鼻内接种铜绿假单胞菌分别感染CPE肠道定植和非定植小鼠, 结果发现肠道CPE定植小鼠的肺损伤更严重, CPE定植加强了支气管和肺泡区域的炎症浸润, 增加了出血面积, 促进了肺泡壁增厚和支气管上皮病变. 这一肠道菌群失调与肺部感染之间的肠-肺轴关系, 可能与微生物代谢产物短链脂肪酸有关[49].

2.2.3 肺炎克雷伯菌

肺炎克雷伯菌(*Klebsiella pneumoniae*)是CAP和HAP的常见病原体, 容易发生耐药, 目前其感染导致的发病率和死亡率很高. 鼻腔接种肺炎克雷伯菌致肺部感染致脓毒症小鼠模型发现, 在整个感染过程中, 肺部微生物群的α多样性无明显变化, 而β多样性发生了改变. 随着肺炎克雷伯菌载量的增加, 链球菌相对丰度减少, 口腔微生物群无明显变化, 而不同时间点的肠道菌群存在一定差异[50]. 肺炎克雷伯菌肺部感染的小鼠肠道中产短链脂肪酸的罗伊氏乳杆菌(*Lactobacillus reuteri*)和假长双歧杆菌(*Bifidobacterium pseudolongum*)的丰度均降低, 感染组中短链脂肪酸的水平减少, 口服补充短链脂肪酸可降低对肺炎克雷伯菌感染的易感性[51]. 这些研究提示了呼吸道菌群与肠道菌群之间存在关联.

2.2.4 嗜肺军团菌

嗜肺军团菌(*Legionella pneumophila*)在胞内复制, 可导致严重的军团病[52]. 军团菌病人的痰液中未观察到嗜肺军团菌占主导地位[53], 但在肺泡灌洗液中可以观察到该病原体的富集[54]. 对于军团菌阳性的痰液样本, 低军团菌丰度的样本以链球菌占主导地位, 而在军团菌丰度高的样本中, 微生物丰富度和多样性更高, 不动杆菌(*Acinetobacter*)和链球菌同时占主导地位[53]. 在军团菌长期治疗期间, 未发现抗生素耐药性基因与持续感染有关, 因此微环境的失调和机会致病菌的增多导致军团菌持续感染的可能性更大[55].

2.3 其他类型感染中呼吸道微生物组的变化特征

典型细菌和病毒感染之外的其他类型呼吸道感染微生物组研究较少. 一项小型非结核分支杆菌(*non-tuberculous Mycobacteria*, NTM)患者队列研究发现, 下呼吸道炎症细胞因子水平与口腔共生菌在下呼吸道的相对丰度有关, 与分枝杆菌的丰度无关[56]. 结核患者常常需要长程抗生素治疗, 有可能对呼吸道微生物组产生不良影响. 有研究评估了6种抗结核方案对呼吸道菌群的影响, 发现利福平(rifampicin)、异烟肼(isoniazid)、吡嗪酰胺(pyrazinamide)和莫西沙星(moxifloxacin)组合对呼吸道菌群影响最小[57]. 痰液中假单胞菌属的富集与抗结核治疗效果不佳相关[58]. 婴儿链球菌在利福平敏感组和耐药组中表现出差异, 这可能与该菌的定植抗性较强有关, 保护了宿主免受其他微生物的侵害[59].

肺炎支原体(*Mycoplasma pneumoniae*)是一种无细胞壁的原核细胞, 5岁以上儿童易感[60]. 它可通过直接竞争或激活宿主的细胞因子来抑制其他细菌的生长, 导致细菌多样性降低[61]. 肺炎支原体在下呼吸道中成为优势菌、微生物多样性降低也意味着肺炎支原体肺炎(mycoplasmal pneumonia, MPP)的严重程度升高[62,63]. 研究发现, MPP 患者鼻咽和口咽样本中微生物群变化具有一致性[64], 这进一步证实了微量吸入和黏液散播是下呼吸道微生物主要来源. 然而, 微生物菌群失调与肺炎发病或黏液栓形成之间的因果关系仍然未明.

肺部的侵入性真菌感染, 包括侵入性肺曲霉病、肺囊虫肺炎和隐球菌病, 每年在全球范围内超过100万例, 主要影响免疫功能低下的个体. 有关肺部真菌感染后呼吸道微生物组变化的报道较少, 有研究报道了一种改良的细菌毒素(LTK63), 通过提高鼻黏膜中病原体特异性$CD8^+$ T细胞和IgA数量, 增强机体对新型隐球菌的免疫应答[65]. 白色念珠菌是人类抗真菌Th17细胞的主要直接诱导剂, 其他真菌引起Th17反应主要通过与白色念珠菌的交叉反应, 肠道中具有保护作用的抗白色念珠菌Th17反应与急性过敏性支气管肺曲霉病等肺部炎症之间存在直接联系. 呼吸道共生微生物中真菌含量少, 对真菌的研究还有待进一步探索[66].

3 呼吸道微生物组作为呼吸道感染的标志物

呼吸道微生物组可以作为呼吸道感染的诊断和预后标识物(表1). 在健康个体中, 肺部核心微生物主要为普雷沃菌、链球菌、韦荣菌、梭杆菌、和嗜血杆菌等五种细菌. 在急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)和医院获得性肺炎患者中, 呼吸道微生物核心菌群的相对丰度较健康对照组降低(分别为34%和43%). 危重病患者中梭杆菌、韦荣菌和普雷沃菌的相对丰度较低, 而嗜血杆菌的相对丰度显著增加. 有53%的患者观察到了假单胞菌(*Pseudomonas*), 其平均相对丰度达到5.3%. 最近一项包含了300多名机械通气患者的大型研究也表明, 下呼吸道葡萄球菌(*Staphylococcus*)和假单胞菌(*Pseudomonas*)富集与下呼吸道炎症增加和临床结局较差有关, 包括30 d生存率较低以及机械通气时间更长[67]. 另一项研究分析了142名机械通气的COVID-19患者呼吸道微生物组, 发现下呼吸道微生物的组成与患者的临床预后密切相关, 特别是唾液支原体(*Mycoplasma salivarium*)的富集与更差的临床预后相关, 包括更高的死亡率和更长的机械通气时间[68].

机械通气可以为细菌繁殖创造良好环境, 易造成重症监护室(intensive care unit, ICU)气管插管患者的微生物定植[73]. α多样性和保护性菌株丰度的下降与患者30 d存活率下降、插管时间延长和病情严重程度显著相关[67,69,74]. 插管时口咽部芽孢杆菌(*Bacilli*)数量较少与呼吸机相关肺炎(ventilator associated pneumonia, VAP)发生风险较高有关[70]. 气管抽吸物中链球菌越多, 患者存活时间越长[71]. 铜绿假单胞菌的存在也与死亡率有关[72].

COVID-19研究也发现, 患者入院时的上呼吸道中的副溶血链球菌(*S. parasanguinis*)与患者良好预后显著相关[16]. 严重COVID-19患者的口腔双歧杆菌、乳酸杆菌和梭菌减少, 口腔双歧杆菌的丰度与COVID-19生物标志物白介素17F和单核细胞趋化蛋白-1(monocyte chemotactic protein-1, MCP-1)的血浆浓度呈负相关[75]. 针对COVID-19患者上呼吸道样本纵向采样结果也显示, 上呼吸道微生物在疾病过程中表现出显著的异质性. α多样性降低和多种病原体或潜在致病菌(包括不动杆菌和念珠菌)的富集, 与疾病进展和更差的临床结局相关, 潜在致病菌丰度与炎症指标浓度和死亡率密切相关[76]. 但在COVID患者康复后, 康复患者的细菌和真菌多样性几乎恢复正常. 一些特定细菌和真菌, 主要是机会性致病菌, 在康复患者中的相对丰度减少, 而产丁酸盐细菌的丰度增加[77].

下呼吸道微生物组与ICU患者预后的相关性在另一项研究中得到验证, 该研究在入院24 h内对91名重症患者的肺部进行支气管肺泡灌洗(broncho-alveolar lavage fluid, BALF)取样. 结果显示, 细菌载量增加的患者机械通气天数更长, 即使在控制肺炎和疾病严重程度等混杂因素后, 这一结果仍然显著. 肺部菌群的构成能够预测机械通气脱机天数, 并且主要受肠道来源相关细菌的影响. 该研究进一步证明, 肺部微生物群的两个关键特征, 细菌负荷和肠道相关细菌在肺部的富集, 可以作为预测ICU患者不良结局的标识物[69]. 2016年

表 1 与临床结局相关的微生物

Table 1 Microorganisms associated with clinical outcomes

微生物类别	人群	样本	关联指标	参考文献
葡萄球菌 假单胞菌	机械通气患者	气管抽吸物	葡萄球菌(*Staphylococcus*)或假单胞菌(*Pseudomonas*)相对丰度越高, 机械通气患者30 d生存率更低以及机械通气时间更长	[67]
唾液支原体	机械通气的重症COVID-19患者	支气管肺泡灌洗	唾液支原体(*Mycoplasma salivarium*)的富集与更高的死亡率和更长的机械通气时间相关	[68]
毛螺菌科 肠杆菌科	机械通气的ICU患者	支气管肺泡灌洗	检测到毛螺菌科(*Lachnospiraceae*)和肠杆菌科(*Enterobacteriaceae*)的存在, ICU患者无呼吸机天数减少, 临床结局更差	[69]
芽孢杆菌	机械通气患者	口咽分泌物	插管时口咽部芽孢杆菌(*Bacilli*)数量较少与呼吸机相关肺炎(VAP)发病的可能性较高有关	[70]
链球菌	机械通气的ICU患者	气管内抽吸物	高丰度链球(*Streptococci*)菌与28 d内生存率相关	[71]
铜绿假单胞菌	机械通气的ICU患者	气管内抽吸物	铜绿假单胞菌(*Pseudomonas aeruginosa*)的存在与患者生存负相关	[72]
副溶血链球菌	COVID19患者	口咽拭子	高丰度副溶血链球菌(*S. parasanguinis*)与患者生存相关	[16]

的一项研究同样发现，肠道相关细菌在下呼吸道的富集与肺泡肿瘤坏死因子(tumor necrosis factor, TNF)的浓度相关，而肺泡TNF是ARDS肺泡炎症的关键介质[78]. 在死亡的COVID-19患者中，宿主抗病毒相关的基因表达显著降低, 机会性细菌和真菌丰度升高. 除了细菌，肺部BALF样本中真菌负荷增加与ARDS患者拔管成功的可能性负相关，微生物载量还与TNF-α等促炎因子正相关[20].

4 呼吸道感染中宿主与呼吸道微生物的互作机制

4.1 健康共生菌会占据生态位, 促进定植抗性

呼吸道共生菌群能够占据其他空置的生态位，从而抵抗外来病原体的定植. 共生菌群通过分泌抗菌因子、与入侵的病原体竞争膜表面的黏附受体以及营养物质等方式，限制入侵物种黏附、复制、传播以及引发疾病的机会. 例如，人鼻腔中定植的里昂葡萄球菌(*Staphylococcus lugdunensis*)会分泌路邓素(lugdunin)来抑制金黄色葡萄球菌(*Staphylococcus aureus*)的黏附[79]. 链霉菌(*Streptomyces*)能够产生氨基糖苷类、碳青霉烯类、氯霉素等抗生素[35]. 脂质依赖性的拥挤棒状杆菌(*Corynebacterium accolens*)通过将皮肤表面的三酰甘油水解为游离脂肪酸，从而对肺炎链球菌产生杀菌作用[80]. 鼻腔中的罗氏菌通过分泌一种能裂解卡他莫拉菌肽聚糖的酶, 限制其定植[81]. 此外, 定植于鼻咽部的狡诈球菌和棒状杆菌可抵御金黄色葡萄球菌和肺炎链球菌的侵袭[82]. 鼻腔中的表皮葡萄球菌(*Staphylococcus epidermidis*)可引起小鼠肺部中性粒细胞和单核细胞聚集, 这一过程由甘油醛-3-磷酸脱氢酶(glyceraldehyde-3-phosphate dehydrogenase, GAPDH)蛋白介导, 可抵御肺炎克雷伯氏菌、鲍曼不动杆菌(*Acinetobacter baumannii*)和甲型流感病毒的侵袭[83]. 同时细菌自身也会改变其所处的生态位的微环境，如肠道中的拟杆菌(*Bacteroidetes*)和丙酸杆菌可以产生短链脂肪酸，这些脂肪酸不仅可以直接抑制肠道中病原体的生长和毒力基因的表达，还可以通过环境酸化间接调节细菌的生长环境[84].

在呼吸道感染期间，呼吸道微生物组的稳态被打破，其多样性和细菌载量产生波动，引发菌群之间互作，如肺炎链球菌可以产生过氧化氢及其他抗菌化合物直接抑制金黄色葡萄球菌的生长[85]. 然而, 也有文献报道，肺炎链球菌与金黄色葡萄球菌之间存在共同定植现象，且肺炎链球菌疫苗的应用并不会导致上呼吸道中的金黄色葡萄球菌发生明显变化[86,87]. 肺炎链球菌与鼻咽部普雷沃菌或肠杆菌的某些蛋白匹配，这些蛋白质可能会促进肺炎链球菌的入侵[88]. 金黄色葡萄球菌入侵时，其胞外DNA与气道定植的副溶血链球菌蛋白BapA1共同参与了二者的生物膜生成，从而增强了金黄色葡萄球菌的定植[89]. 群体感应是细菌间通过产生和感知信号分子进行交流的一种方式[90]. 铜绿假单胞菌通过群体感应调节生物膜形成、病原体运动和毒力因子, 从而促进其致病作用[91]. 肠道中存在可以直接调节宿主表型的潜在基石物种，如克里斯滕氏菌(*Christensenellaceae*)[92]，但此类细菌在肺部尚未被发现. 在新生儿的研究中发现, 高丰度的莫拉氏菌和棒状杆菌/狡诈球菌与呼吸道感染率较低相关[93]，这可能预示着肺部存在某种核心微生物模式，在感染中起到定植抗性的核心作用.

4.2 呼吸道微生物与宿主免疫互作机制

小鼠肺部免疫与肺微生物组有关. 研究发现, 肺部的IL-1α和IL-4浓度与菌群多样性之间存在负相关关系[94]. 在适应性免疫功能受损的小鼠中, 肺部共生菌如梭状芽孢杆菌和拟杆菌的数量会增加. 而在先天性和适应性免疫系统均缺陷的小鼠中, 变形杆菌(*Proteobacteria*)的丰度会增加[95].

免疫耐受是指在抗原刺激下，免疫系统不产生应答或应答力下降的现象，这可能部分解释了共生菌如何能够在不受免疫系统攻击的情况下与宿主共存. 肠道微生物能够刺激幼稚T细胞上调Foxp3基因，从而在结肠部位分化成以视黄酸相关孤儿受体γt(RORγt)标记的外周Treg(pTreg)细胞, Treg细胞在调节肠道微生物免疫耐受中发挥着重要作用. 相反，缺乏pTreg细胞的小鼠会导致Th2和Th17相关的炎症增加[96]. 在呼吸道领域，免疫耐受的研究相对较少，尤其是针对新生儿. 微生物对免疫系统的成熟具有影响，二者之间的相互作用决定了生命早期的免疫耐受或抵抗能力的形成[97].

疾病耐受性是指宿主疾病状态下受损程度降低的现象. 当细菌入侵肺泡时, 肺泡巨噬细胞会通过科恩孔(Kohn's holes)吞噬细菌，从而避免中性粒细胞的招募和诱发炎症反应[98]. 细菌也可通过间接减弱免疫反应介导疾病耐受[99]. 肺炎克雷伯氏菌(*Klebsiella pneumo-*

niae)ST258能够改变宿主的代谢反应, 在葡萄糖耗竭后增强谷氨酰胺代谢和脂肪酸β氧化, 导致肺部活性氧化物含量增加, 招募免疫抑制细胞, 促进抗炎因子分泌, 延长病原体存活时间, 这一过程受宿主IRG1基因上调介导. IRG1编码一种调节衣康酸生成的酶, 衣康酸在免疫耐受和训练免疫(指由表观遗传学和细胞生理学调控的先天免疫记忆)中至关重要[100].

4.3 感染产生局部或全身性炎症反应, 促进细菌易位

病毒感染会降低上皮的完整性并促进细菌易位[101]. 病毒感染可直接损伤纤毛细胞, 降低黏膜纤毛清除能力, 导致上皮剥脱[102], 暴露纤连蛋白, 从而使肺炎链球菌, 金黄色葡萄球菌和化脓性链球菌等病原体得以黏附[102~104]. 除了纤连蛋白外, 病毒感染还会导致细胞间黏附分子1(intercellular adhesion molecule, ICAM-1)、癌胚抗原相关细胞黏附分子1(carcinoembryonic antigen-related cell adhesion molecule 1, CEACAM-1)和血小板活化因子(platelet-activating factor receptor, PAF-r)等表面分子或细胞受体的上调, 这也进一步增强了细菌的黏附能力[105].

除此之外, 感染可诱发黏膜炎症, 直接影响先天免疫和适应性免疫, 从而对呼吸道微生物组产生影响. 在固有免疫层面, 病毒感染会导致中性粒细胞功能受损[106,107], 促进NK细胞活化和募集[108], 并引发单核细胞的募集及其向巨噬细胞的活化, 同时还会导致细胞因子谱的改变[16,109]. Iwasaki及其团队[110]发现, 在流感病毒感染期间, 接受多次抗生素治疗的小鼠表现出炎症小体组分的表达减少, 以及$CD4^+$ T细胞、$CD8^+$ T细胞和B细胞的免疫反应受损. 这些变化可能导致对病原体的定植抗性降低, 从而增加病毒与细菌双重感染的风险.

流感病毒诱导的炎症可导致富含唾液酸的黏蛋白(如Muc5AC)的表达增加, 从而促进肺炎链球菌的增殖[111]. 体内研究也显示, 呼吸道病毒感染会促进成人和儿童病原体定植[112,113]. 宿主对流感感染的应答可能会间接影响呼吸道中抗生素抗性基因的表达, 特定的宿主基因模块与微生物群落的组成之间也存在相关性. 例如, 嗜酸维氏菌科(*Veillonellaceae*)是呼吸道中常见的细菌家族之一, 它与宿主对病毒和细菌侵袭应答的基因模块呈正相关, 比如I型干扰素信号传导等. 在流感患者中, 约有25%的抗生素抗性基因来源于肺炎链球菌和金黄色葡萄球菌[114].

4.4 细菌病原体的存在会增加病毒的黏附和复制

流感嗜血杆菌已被证明可以诱导气道上皮细胞ICAM-1和TLR3受体的表达, 从而增强了鼻病毒的黏附并刺激了鼻病毒诱导的趋化因子产生[115]. 最近的一项体外研究也表明, 流感嗜血杆菌同样增加了呼吸道合胞病毒的复制, 这与促炎细胞因子IL-6和IL-8的释放有关, 这表明特定的细菌群落成员可以加重病毒感染的炎症反应[116]. 此外, 人支气管上皮细胞与肺炎链球菌预孵育后, 其对人偏肺病毒感染的易感性也会增加[117].

5 呼吸道微生物组用于呼吸道感染干预的临床前研究

5.1 对呼吸道感染认识的改变

基于呼吸道微生物组的诊断工具可能具有重要的潜在诊断价值. 通过严格匹配的病例对照研究设计, 在新生儿[118]和成年人[119]中的研究表明, 利用鼻咽部细菌和病毒的组成构建分类器, 可以准确识别下呼吸道感染. 这提示了呼吸道感染的临床表现可能是由呼吸道微生物, 宿主因素(如年龄、解剖结构、黏膜炎症、先天和适应性免疫状态、遗传背景)以及环境特征共同驱动, 而不仅仅是由单一病原体的特征决定. 因此, 临床治疗决策不应仅基于临床表型, 还应综合考虑宿主个体差异, 微生物组特征以及疾病的严重程度[120]. 将病原和宿主反应特征相结合的诊断方法[121], 有望极大地改变临床决策, 提高治疗效果.

5.2 抗生素及益生菌的应用

抗生素作为呼吸道感染的常规临床治疗手段, 其对呼吸道微生物组的影响并不总是有利的. 例如, 长期使用大环内酯类药物可显著改变下呼吸道微生物的组成[122,123], 使用新霉素治疗的小鼠相比对照组更容易感染流感[110]. 此外, 抗生素的使用会导致选择压力. 一项研究比较了健康人和中重度 COVID-19患者口咽微生物组成和相关功能变化[124], 结果显示, COVID-19 患者中富集的致病病原体具有更高的毒力和耐药性, 这表明抗生素的使用可能使疾病更加难以控制. 因此, 在临床诊疗过程中应慎重考虑抗生素的应用.

益生菌作为菌群调节的常用手段, 在当前的微生物疗法中占据重要地位. 其中, 通过口服益生菌的方式, 利用肠-肺或肠-呼吸轴的相互作用来调节气道反

应, 已成为一种主流策略[125]. 一项针对COVID-19患者的小规模临床研究表明, 采用乳酸菌进行口腔微生物治疗有助于降低呼吸衰竭的风险[126]. 进一步地, ClinicalTrials.gov上已有多项临床试验注册(如NCT04363372、NCT04368351、NCT04458519等), 旨在研究益生菌(如乳杆菌或双歧杆菌)在预防或治疗呼吸道病毒感染方面的效果. 这些临床试验的开展, 不仅体现了科学界对益生菌潜在临床价值的认可, 也预示着未来可能带来的显著临床和经济效益.

相比于通过口服益生菌经肠-肺轴间接影响呼吸健康的方式, 直接将微生物应用于呼吸道, 在感染部位发挥活性, 可能更有效地调节呼吸道感染的易感性和病程. 已有研究展示了这种局部应用策略的有效性. 例如, 流感嗜血杆菌裂解物的单次预防性雾化治疗成功预防了流感肺炎的发生[127], 而鼻内注射发酵乳酸杆菌CJL-112L则在小鼠流感感染模型中促进了特异性保护性IgA的产生, 增强了免疫防御[128]. 乳酸杆菌因其多种益生特性和在气道局部应用的潜力, 被视为极有希望的候选菌株[129,130], 目前已经有几项研究证明了其气道施用的可行性和安全性[130,131]. 一项对COVID-19患者鼻腔使用益生菌的临床试验(NCT04458519)也已经完成. 尽管如此, 在临床实践中, 如何确定最佳的益生菌菌株、混合物、剂量和配方仍是一个挑战. 这需要精心设计的临床试验来评估不同策略的效果, 并考虑到个体差异、疾病状态以及呼吸道菌群的复杂性和动态变化. 此外, 微生物的代谢物作为菌群与宿主对话的关键信号, 也展现出作为治疗肺部感染巨大潜力[132]. 肠道中菌源的宿主同工酶的发现为代谢性疾病提供了新的治疗思路[133], 提示我们呼吸道中可能也存在类似机制, 但其具体存在和作用机制尚需进一步深入探究.

5.3 人微生物组的整体性

肠道微生物组在呼吸道感染的治疗中也扮演了重要角色. 多项研究已经揭示了肠道微生物组与呼吸道感染之间的紧密联系, 包括其在COVID-19病例与健康对照之间的区分能力以及预测疾病进展的潜力[134]. 这些发现不仅加深了我们对肠道-肺部微生物组相互作用的理解, 还启发了通过调控肠道微生物来影响肺部健康的新策略. 具体而言, 肠道微生物组中的某些特定成分, 如环形梭菌(*Clostridium orbiscindens*)产生的去胺基酪胺酸(dopamine transporter, DAT), 能够启动I型干扰素(interferon, IFN)信号通路转导, 从而减少肺部免疫病理损伤, 保护宿主免受流感等呼吸道病毒的侵害[135]. 肠道微生物组还能增强宿主在感染期间的适应性免疫反应[136], 如远端(直肠)注射Toll样受体激动剂可以在小鼠模型中逆转抗生素治疗导致的$CD4^+$ T、$CD8^+$ T和B细胞免疫缺陷[110]. 口服大分子多糖等特定物质能够调节肺-肠轴中Th17/Treg细胞的平衡, 从而改善甲型流感感染的小鼠的肺损伤情况[137].

Leon Hosang团队[138]提出, 肺部流感感染可能会改变肺部微生物的组成, 产脂多糖(lipopolysaccharide, LPS)的细菌群体增加, 进而影响脑中小胶质细胞的激活状态. 流感病毒和肺炎链球菌双重感染会增加“活化”的变形小胶质细胞数量和下丘脑中的炎性细胞因子表达[139]. 这些研究进一步强调了人体微生物组作为一个统一整体, 在不同器官系统中的相互作用和影响, 为未来的治疗策略提供了全新的视角.

6 总结与展望

呼吸道微生物组研究在近年来已经获得重要进展, 目前已经明确上下呼吸道各解剖区间的主要微生物类群. 呼吸道感染常常伴随着菌群多样性的下降, 微生物载量升高和机会病原菌的丰度升高, 特别是在ICU患者中, 已观察到多种细菌的丰度与患者预后相关. 尽管目前对疾病状态下的呼吸道微生物组研究已经可以识别出与鉴别诊断、疾病严重程度和预后相关的微生物特征. 然而, 不同研究结果之间缺乏一致性, 使得明确定义呼吸道微生物组失调(dysbiosis)变得困难. 即使在单一疾病过程中, 可能也存在多种形式的失调, 不同队列、不同感染类型, 和不同疾病进展中呼吸道微生物组的失调的表型不一致, 使得发现呼吸道微生物组共性标识物充满挑战. 未来的研究需要从横断面设计和相关性研究转向纵向采样方法, 考虑地理特征和实验条件, 建立能高度模拟人体呼吸道微生物组的动物模型, 更好地控制微生物和宿主条件验证微生物作用机制.

与肠道微生物组不同, 肠道益生菌可以用来调控胃肠道菌群, 实现对代谢性疾病的治疗, 改善对抗肿瘤药物的响应, 但目前还没有在呼吸道局部使用益生菌来调控呼吸道菌群, 达到干预呼吸道感染疾病的明确证据. 尽管在多个动物实验中[47,48], 间歇性滴入口腔共生菌到下呼吸道改变了宿主对呼吸道病原体的易感性, 但目前这个领域仍缺乏机制性的研究和可行性的实施方案, 目前难以实施安全和有意义的临床试验.

总之, 呼吸道微生物组是一个动态变化的群体, 呼吸道微生物组为认知呼吸道感染提供了一个新的视角, 它与宿主的免疫状态和多种呼吸道感染的发生发展密切相关, 且作用机制值得未来深入地研究.

参考文献

1 England R J A, Homer J J, Knight L C, et al. Nasal pH measurement: a reliable and repeatable parameter. Clin Otolaryngol, 1999, 24: 67–68
2 Brunworth J D, Garg R, Mahboubi H, et al. Detecting nasopharyngeal reflux: a novel pH probe technique. Ann Otol Rhinol Laryngol, 2012, 121: 427–430
3 Man W H, de Steenhuijsen Piters W A A, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol, 2017, 15: 259–270
4 Keck T, Lindemann J. Numerical simulation and nasal air-conditioning. GMS Curr Top Otorhinolaryngol Head Neck Surg, 2010, 9: doc08
5 Natalini J G, Singh S, Segal L N. The dynamic lung microbiome in health and disease. Nat Rev Microbiol, 2023, 21: 222–235
6 Zhou X, Shen X, Johnson J S, et al. Longitudinal profiling of the microbiome at four body sites reveals core stability and individualized dynamics during health and disease. Cell Host Microbe, 2024, 32: 506–526.e9
7 Zhang J, Wu Y, Liu J, et al. Differential oral microbial input determines two microbiota pneumo-types associated with health status. Adv Sci, 2022, 9: 2203115
8 Ma Z, Zuo T, Frey N, et al. A systematic framework for understanding the microbiome in human health and disease: from basic principles to clinical translation. Signal Transduct Target Ther, 2024, 9: 237
9 Hernández-Terán A, Mejía-Nepomuceno F, Herrera M T, et al. Dysbiosis and structural disruption of the respiratory microbiota in COVID-19 patients with severe and fatal outcomes. Sci Rep, 2021, 11: 21297
10 Rueca M, Fontana A, Bartolini B, et al. Investigation of nasal/oropharyngeal microbial community of COVID-19 patients by 16S rDNA sequencing. Int J Environ Res Public Health, 2021, 18: 2174
11 Bradley E S, Zeamer A L, Bucci V, et al. Oropharyngeal microbiome profiled at admission is predictive of the need for respiratory support among COVID-19 patients. Front Microbiol, 2022, 13: 1009440
12 de Castilhos J, Zamir E, Hippchen T, et al. Severe dysbiosis and specific *Haemophilus* and *Neisseria* signatures as hallmarks of the oropharyngeal microbiome in critically ill coronavirus disease 2019 (COVID-19) patients. Clin Infect Dis, 2022, 75: e1063–e1071
13 Merenstein C, Liang G, Whiteside S A, et al. Signatures of COVID-19 severity and immune response in the respiratory tract microbiome. mBio, 2021, 12: e01777-21
14 Liu G, Tang C M, Exley R M. Non-pathogenic *Neisseria*: members of an abundant, multi-habitat, diverse genus. Microbiology, 2015, 161: 28
15 Ma S, Zhang F, Zhou F, et al. Metagenomic analysis reveals oropharyngeal microbiota alterations in patients with COVID-19. Sig Transduct Target Ther, 2021, 6: 191
16 Ren L, Wang Y, Zhong J, et al. Dynamics of the upper respiratory tract microbiota and its association with mortality in COVID-19. Am J Respir Crit Care Med, 2021, 204: 1379–1390
17 Babenko V, Bakhtyev R, Baklaushev V, et al. Analysis of the upper respiratory tract microbiota in mild and severe COVID-19 patient. bioRxiv, 2021, https://doi.org/10.1101/2021.09.20.461025
18 Feehan A K, Rose R, Nolan D J, et al. Nasopharyngeal Microbiome community composition and structure is associated with severity of COVID-19 disease and breathing treatment. Appl Microbiol, 2021, 1: 177–188
19 Chen J, Liu X, Liu W, et al. Comparison of the respiratory tract microbiome in hospitalized COVID-19 patients with different disease severity. J Med Virol, 2022, 94: 5284–5293
20 Kullberg R F J, de Brabander J, Boers L S, et al. Lung microbiota of critically ill patients with COVID-19 are associated with nonresolving acute respiratory distress syndrome. Am J Respir Crit Care Med, 2022, 206: 846–856
21 Tsang T K, Lee K H, Foxman B, et al. Association between the respiratory microbiome and susceptibility to influenza virus infection. Clin Infect Dis, 2020, 71: 1195–1203
22 Huffnagle G B, Dickson R P, Lukacs N W. The respiratory tract microbiome and lung inflammation: a two-way street. Mucosal Immunol, 2017, 10: 299–306
23 Li H, Wu X, Zeng H, et al. Unique microbial landscape in the human oropharynx during different types of acute respiratory tract infections. Microbiome, 2023, 11: 157
24 Ding T, Song T, Zhou B, et al. Microbial composition of the human nasopharynx varies according to influenza virus type and vaccination status. mBio, 2019, 10: e01296-19
25 Jobran S, Kattan R, Shamaa J, et al. Adenovirus respiratory tract infections in infants: a retrospective chart-review study. Lancet, 2018, 391: S43
26 Zhong H, Dong X. Analysis of clinical characteristics and risk factors of severe adenovirus pneumonia in children. Front Pediatr, 2021, 9: 566797

27 Zhou W, Chen J, Xi Z, et al. Characteristics of lung microbiota in children's refractory *Mycoplasma pneumoniae* pneumonia coinfected with human adenovirus B. Canadian J Infect Dis Med Microbiol, 2022, 2022: 1–8

28 Wang H, Zhou Q, Dai W, et al. Lung microbiota and pulmonary inflammatory cytokines expression vary in children with tracheomalacia and adenoviral or *Mycoplasma pneumoniae* pneumonia. Front Pediatr, 2019, 7: 265

29 Yang J, Hooper W C, Phillips D J, et al. Cytokines in *Mycoplasma pneumoniae* infections. Cytokine Growth Factor Rev, 2004, 15: 157–168

30 de Steenhuijsen Piters W A A, Heinonen S, Hasrat R, et al. Nasopharyngeal microbiota, host transcriptome, and disease severity in children with respiratory syncytial virus infection. Am J Respir Crit Care Med, 2016, 194: 1104–1115

31 Kanmani P, Clua P, Vizoso-Pinto M G, et al. Respiratory commensal bacteria *Corynebacterium pseudodiphtheriticum* improves resistance of infant mice to respiratory syncytial virus and *Streptococcus pneumoniae* superinfection. Front Microbiol, 2017, 8: 1613

32 Nakagome K, Bochkov Y A, Ashraf S, et al. Effects of rhinovirus species on viral replication and cytokine production. J Allergy Clin Immunol, 2014, 134: 332–341.e10

33 Lehtinen M J, Hibberd A A, Männikkö S, et al. Nasal microbiota clusters associate with inflammatory response, viral load, and symptom severity in experimental rhinovirus challenge. Sci Rep, 2018, 8: 11411

34 Kloepfer K M, Sarsani V K, Poroyko V, et al. Community-acquired rhinovirus infection is associated with changes in the airway microbiome. J Allergy Clin Immunol, 2017, 140: 312–315.e8

35 Dickson R P, Erb-Downward J R, Huffnagle G B. Towards an ecology of the lung: new conceptual models of pulmonary microbiology and pneumonia pathogenesis. Lancet Respir Med, 2014, 2: 238–246

36 Fenn D, Abdel-Aziz M I, van Oort P M P, et al. Composition and diversity analysis of the lung microbiome in patients with suspected ventilator-associated pneumonia. Crit Care, 2022, 26: 203

37 Du S, Wu X, Li B, et al. Clinical factors associated with composition of lung microbiota and important taxa predicting clinical prognosis in patients with severe community-acquired pneumonia. Front Med, 2022, 16: 389–402

38 Pérez-Cobas A E, Ginevra C, Rusniok C, et al. The respiratory tract microbiome, the pathogen load, and clinical interventions define severity of bacterial pneumonia. Cell Rep Med, 2023, 4: 101167

39 Musher D M, Jesudasen S J, Barwatt J W, et al. Normal respiratory flora as a cause of community-acquired pneumonia. Open Forum Infect Dis, 2020, 7: ofaa307

40 Corrêa R A, Costa A N, Lundgren F, et al. 2018 recommendations for the management of community acquired pneumonia. J bras pneumol, 2018, 44: 405–423

41 Gierse L C, Meene A, Skorka S, et al. Impact of pneumococcal and viral pneumonia on the respiratory and intestinal tract microbiomes of mice. Microbiol Spectr, 2023, 11: e03447-22

42 Dockrell D H, Whyte M K B, Mitchell T J. Pneumococcal pneumonia. Chest, 2012, 142: 482–491

43 O'Brien K L, Baggett H C, Brooks W A, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet, 2019, 394: 757–779

44 Nannapaneni P, Sundh J, Prast-Nielsen S, et al. Metatranscriptomics of nasopharyngeal microbiota and host distinguish between pneumonia and health. Am J Respir Crit Care Med, 2022, 206: 1564–1567

45 Perez A C, Pang B, King L B, et al. Residence of *Streptococcus pneumoniae* and *Moraxella catarrhalis* within polymicrobial biofilm promotes antibiotic resistance and bacterial persistence *in vivo*. Pathogens Dis, 2014, 70: 280–288

46 Armbruster C E, Hong W, Pang B, et al. Indirect pathogenicity of *Haemophilus influenzae* and *Moraxella catarrhalis* in polymicrobial otitis media occurs via interspecies quorum signaling. mBio, 2010, 1: e00102-10

47 Wu B G, Sulaiman I, Tsay J C J, et al. Episodic aspiration with oral commensals induces a MyD88-dependent, pulmonary T-helper cell type 17 response that mitigates susceptibility to *Streptococcus pneumoniae*. Am J Respir Crit Care Med, 2021, 203: 1099–1111

48 Horn K J, Schopper M A, Drigot Z G, et al. Airway *Prevotella* promote TLR2-dependent neutrophil activation and rapid clearance of *Streptococcus pneumoniae* from the lung. Nat Commun, 2022, 13: 3321

49 Le Guern R, Grandjean T, Stabler S, et al. Gut colonisation with multidrug-resistant *Klebsiella pneumoniae* worsens *Pseudomonas aeruginosa* lung infection. Nat Commun, 2023, 14: 78

50 Wolff N S, Jacobs M C, Wiersinga W J, et al. Pulmonary and intestinal microbiota dynamics during Gram-negative pneumonia-derived sepsis. ICMx, 2021, 9: 35

51 Wu T, Xu F, Su C, et al. Alterations in the gut microbiome and cecal metabolome during *Klebsiella pneumoniae*-induced pneumosepsis. Front Immunol, 2020, 11: 1331

52 Abu Kwaik Y, Gao L Y, Stone B J, et al. Invasion of protozoa by *Legionella pneumophila* and its role in bacterial ecology and pathogenesis. Appl Environ Microbiol, 1998, 64: 3127–3133

53 Mizrahi H, Peretz A, Lesnik R, et al. Comparison of sputum microbiome of legionellosis-associated patients and other pneumonia patients: indications for polybacterial infections. Sci Rep, 2017, 7: 40114

54 Pérez-Cobas A E, Ginevra C, Rusniok C, et al. Persistent Legionnaires' disease and associated antibiotic treatment engender a highly disturbed

pulmonary microbiome enriched in opportunistic microorganisms. mBio, 2020, 11: e00889-20
55 Pouderoux C, Ginevra C, Descours G, et al. Slowly or nonresolving Legionnaires' disease: case series and literature review. Clin Infect Dis, 2020, 70: 1933–1940
56 Sulaiman I, Wu B G, Li Y, et al. Evaluation of the airway microbiome in nontuberculous mycobacteria disease. Eur Respir J, 2018, 52: 1800810
57 Musisi E, Wyness A, Eldirdiri S, et al. Effect of seven anti-tuberculosis treatment regimens on sputum microbiome: a retrospective analysis of the HIGHRIF study 2 and PanACEA MAMS-TB clinical trials. Lancet Microbe, 2023, 4: e913–e922
58 Wu J, Liu W, He L, et al. Sputum microbiota associated with new, recurrent and treatment failure tuberculosis. PLoS One, 2013, 8: e83445
59 Cai X, Luo Y, Zhang Y, et al. Airway microecology in rifampicin-resistant and rifampicin-sensitive pulmonary tuberculosis patients. BMC Microbiol, 2022, 22: 286
60 Kumar S. *Mycoplasma pneumoniae*. Ind J Med Res, 2018, 147: 23–31
61 Zhou Q, Xie G, Liu Y, et al. Different nasopharynx and oropharynx microbiota imbalance in children with *Mycoplasma pneumoniae* or influenza virus infection. Microb Pathog, 2020, 144: 104189
62 Dai W, Wang H, Zhou Q, et al. The concordance between upper and lower respiratory microbiota in children with *Mycoplasma pneumoniae* pneumonia. Emerg Microbes Infects, 2018, 7: 1–8
63 Wang Y, Yu X, Liu F, et al. Respiratory microbiota imbalance in children with *Mycoplasma pneumoniae* pneumonia. Emerg Microbes Infects, 2023, 12: 2202272
64 Lu Z, Dai W, Liu Y, et al. The alteration of nasopharyngeal and oropharyngeal microbiota in children with MPP and non-MPP. Genes, 2017, 8: 380
65 Salazar F, Bignell E, Brown G D, et al. Pathogenesis of respiratory viral and fungal coinfections. Clin Microbiol Rev, 2022, 35: e00094-21
66 Yan Q, Li S, Yan Q, et al. A genomic compendium of cultivated human gut fungi characterizes the gut mycobiome and its relevance to common diseases. Cell, 2024, 187: 2969–2989.e24
67 Kitsios G D, Yang H, Yang L, et al. Respiratory tract dysbiosis is associated with worse outcomes in mechanically ventilated patients. Am J Respir Crit Care Med, 2020, 202: 1666–1677
68 Sulaiman I, Chung M, Angel L, et al. Microbial signatures in the lower airways of mechanically ventilated COVID-19 patients associated with poor clinical outcome. Nat Microbiol, 2021, 6: 1245–1258
69 Dickson R P, Schultz M J, van der Poll T, et al. Lung microbiota predict clinical outcomes in critically ill patients. Am J Respir Crit Care Med, 2020, 201: 555–563
70 Emonet S, Lazarevic V, Leemann Refondini C, et al. Identification of respiratory microbiota markers in ventilator-associated pneumonia. Intensive Care Med, 2019, 45: 1082–1092
71 Woo S, Park S Y, Kim Y, et al. The dynamics of respiratory microbiota during mechanical ventilation in patients with pneumonia. J Clin Med, 2020, 9: 638
72 Hotterbeekx A, Xavier B B, Bielen K, et al. The endotracheal tube microbiome associated with *Pseudomonas aeruginosa* or *Staphylococcus epidermidis*. Sci Rep, 2016, 6: 36507
73 Perkins S D, Woeltje K F, Angenent L T. Endotracheal tube biofilm inoculation of oral flora and subsequent colonization of opportunistic pathogens. Int J Med Microbiol, 2010, 300: 503–511
74 Lamarche D, Johnstone J, Zytaruk N, et al. Microbial dysbiosis and mortality during mechanical ventilation: a prospective observational study. Respir Res, 2018, 19: 245
75 Kim J G, Zhang A, Rauseo A M, et al. The salivary and nasopharyngeal microbiomes are associated with SARS-CoV-2 infection and disease severity. J Med Virol, 2023, 95: e28445
76 Xie L, Luo G, Yang Z, et al. The clinical outcome of COVID-19 is strongly associated with microbiome dynamics in the upper respiratory tract. J Infect, 2024, 88: 106118
77 Wei N, Zhu G, Zhao T, et al. Characterization of oral bacterial and fungal microbiome in recovered COVID-19 patients. BMC Microbiol, 2023, 23: 123
78 Dickson R P, Singer B H, Newstead M W, et al. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol, 2016, 1: 16113
79 Zipperer A, Konnerth M C, Laux C, et al. Human commensals producing a novel antibiotic impair pathogen colonization. Nature, 2016, 535: 511–516
80 Bomar L, Brugger S D, Yost B H, et al. *Corynebacterium accolens* releases antipneumococcal free fatty acids from human nostril and skin surface triacylglycerols. mBio, 2016, 7: e01725-15
81 Stubbendieck R M, Dissanayake E, Burnham P M, et al. *Rothia* from the human nose inhibit *Moraxella catarrhalis* colonization with a secreted peptidoglycan endopeptidase. mBio, 2023, 14: e00464-23
82 Brugger S D, Eslami S M, Pettigrew M M, et al. *Dolosigranulum pigrum* cooperation and competition in human nasal microbiota. mSphere, 2020, 5: e00852-20

83 Kim G, Lee Y, You J S, et al. A moonlighting protein secreted by a nasal microbiome fortifies the innate host defense against bacterial and viral infections. Immune Netw, 2023, 23: e31

84 Mann E R, Lam Y K, Uhlig H H. Short-chain fatty acids: linking diet, the microbiome and immunity. Nat Rev Immunol, 2024, 24: 577–595

85 Regev-Yochay G, Trzciński K, Thompson C M, et al. Interference between *Streptococcus pneumoniae* and *Staphylococcus aureus*: *in vitro* hydrogen peroxide-mediated killing by *Streptococcus pneumoniae*. J Bacteriol, 2006, 188: 4996–5001

86 Lewnard J A, Givon-Lavi N, Huppert A, et al. Epidemiological markers for interactions among *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* in upper respiratory tract carriage. J Infect Dis, 2016, 213: 1596–1605

87 Quintero B, Araque M, van der Gaast-de Jongh C, et al. Epidemiology of *Streptococcus pneumoniae* and *Staphylococcus aureus* colonization in healthy Venezuelan children. Eur J Clin Microbiol Infect Dis, 2011, 30: 7–19

88 Hathaway L J, Bättig P, Reber S, et al. *Streptococcus pneumoniae* detects and responds to foreign bacterial peptide fragments in its environment. Open Biol, 2014, 4: 130224

89 Gao M, Zuo J, Shen Y, et al. Modeling co-infection by *Streptococcus suis* and *Haemophilus parasuis* reveals influences on biofilm formation and host response. Animals, 2023, 13: 1511

90 Spacapan M, Bez C, Venturi V. Quorum sensing going wild. iScience, 2023, 26: 108000

91 Diggle S P, Griffin A S, Campbell G S, et al. Cooperation and conflict in quorum-sensing bacterial populations. Nature, 2007, 450: 411–414

92 Mettelman R C, Allen E K, Thomas P G. Mucosal immune responses to infection and vaccination in the respiratory tract. Immunity, 2022, 55: 749–780

93 Biesbroek G, Tsivtsivadze E, Sanders E A M, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. Am J Respir Crit Care Med, 2014, 190: 1283–1292

94 Dickson R P, Erb-Downward J R, Falkowski N R, et al. The lung microbiota of healthy mice are highly variable, cluster by environment, and reflect variation in baseline lung innate immunity. Am J Respir Crit Care Med, 2018, 198: 497–508

95 Nunzi E, Renga G, Palmieri M, et al. A shifted composition of the lung microbiota conditions the antifungal response of immunodeficient mice. Int J Mol Sci, 2021, 22: 8474

96 Haase S, Haghikia A, Wilck N, et al. Impacts of microbiome metabolites on immune regulation and autoimmunity. Immunology, 2018, 154: 230–238

97 Brodin P. Immune-microbe interactions early in life: a determinant of health and disease long term. Science, 2022, 376: 945–950

98 Neupane A S, Willson M, Chojnacki A K, et al. Patrolling alveolar macrophages conceal bacteria from the immune system to maintain homeostasis. Cell, 2020, 183: 110–125.e11

99 Martins R, Carlos A R, Braza F, et al. Disease tolerance as an inherent component of immunity. Annu Rev Immunol, 2019, 37: 405–437

100 Domínguez-Andrés J, Novakovic B, Li Y, et al. The itaconate pathway is a central regulatory node linking innate immune tolerance and trained immunity. Cell Metab, 2019, 29: 211–220.e5

101 Sajjan U, Wang Q, Zhao Y, et al. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. Am J Respir Crit Care Med, 2008, 178: 1271–1281

102 Suzuki K, Bakaletz L O. Synergistic effect of adenovirus type 1 and nontypeable *Haemophilus influenzae* in a chinchilla model of experimental otitis media. Infect Immun, 1994, 62: 1710–1718

103 Pittet L A, Hall-Stoodley L, Rutkowski M R, et al. influenza virus infection decreases tracheal mucociliary velocity and clearance of *Streptococcus pneumoniae*. Am J Respir Cell Mol Biol, 2010, 42: 450–460

104 van der Flier M, Chhun N, Wizemann T M, et al. Adherence of *Streptococcus pneumoniae* to immobilized fibronectin. Infect Immun, 1995, 63: 4317–4322

105 Avadhanula V, Rodriguez C A, DeVincenzo J P, et al. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. J Virol, 2006, 80: 1629–1636

106 McNamee L A, Harmsen A G. Both influenza-induced neutrophil dysfunction and neutrophil-independent mechanisms contribute to increased susceptibility to a secondary *Streptococcus pneumoniae* infection. Infect Immun, 2006, 74: 6707–6721

107 Mathew D, Giles J R, Baxter A E, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science, 2020, 369: eabc8511

108 Small C L, Shaler C R, McCormick S, et al. Influenza Infection leads to increased susceptibility to subsequent bacterial superinfection by impairing NK cell responses in the lung. J Immunol, 2010, 184: 2048–2056

109 Hursitoglu M, Isıksacan N, Erismis B, et al. *In-vitro* cytokine production and nasopharyngeal microbiota composition in the early stage of COVID-19 infection. Cytokine, 2022, 149: 155757

110 Ichinohe T, Pang I K, Kumamoto Y, et al. Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc Natl Acad Sci USA, 2011, 108: 5354–5359

111 Siegel S J, Roche A M, Weiser J N. Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. Cell Host Microbe, 2014, 16: 55–67

112 van den Bergh M R, Biesbroek G, Rossen J W A, et al. Associations between pathogens in the upper respiratory tract of young children: interplay between viruses and bacteria. PLoS One, 2012, 7: e47711

113 Molyneaux P L, Mallia P, Cox M J, et al. Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2013, 188: 1224–1231

114 Zhang L, Forst C V, Gordon A, et al. Characterization of antibiotic resistance and host-microbiome interactions in the human upper respiratory tract during influenza infection. Microbiome, 2020, 8: 39

115 Sajjan U S, Jia Y, Newcomb D C, et al. *H. influenzae* potentiates airway epithelial cell responses to rhinovirus by increasing ICAM-1 and TLR3 expression. FASEB J, 2006, 20: 2121–2123

116 Gulraiz F, Rellinghausen C, Bruggeman C A, et al. *Haemophilus influenzae* increases the susceptibility and inflammatory response of airway epithelial cells to viral infections. FASEB J, 2015, 29: 849–858

117 Verkaik N J, Nguyen D T, de Vogel C P, et al. *Streptococcus pneumoniae* exposure is associated with human metapneumovirus seroconversion and increased susceptibility to *in vitro* HMPV infection. Clin Microbiol Infect, 2011, 17: 1840–1844

118 Man W H, van Houten M A, Mérelle M E, et al. Bacterial and viral respiratory tract microbiota and host characteristics in children with lower respiratory tract infections: a matched case-control study. Lancet Respir Med, 2019, 7: 417–426

119 Haak B W, Brands X, Davids M, et al. Bacterial and viral respiratory tract microbiota and host characteristics in adults with lower respiratory tract infections: a case-control study. Clin Infect Dis, 2022, 74: 776–784

120 Lloréns-Rico V, Gregory A C, Van Weyenbergh J, et al. Clinical practices underlie COVID-19 patient respiratory microbiome composition and its interactions with the host. Nat Commun, 2021, 12: 6243

121 Ross M H, Zick B L, Tsalik E L. Host-based diagnostics for acute respiratory infections. Clin Ther, 2019, 41: 1923–1938

122 Taylor S L, Leong L E X, Mobegi F M, et al. Long-term azithromycin reduces *Haemophilus influenzae* and increases antibiotic resistance in severe asthma. Am J Respir Crit Care Med, 2019, 200: 309–317

123 Ritchie A I, Singanayagam A. Metagenomic characterization of the respiratory microbiome. A pièce de résistance. Am J Respir Crit Care Med, 2020, 202: 321–322

124 Wu J, Liu W, Zhu L, et al. Dysbiosis of oropharyngeal microbiome and antibiotic resistance in hospitalized COVID-19 patients. J Med Virol, 2023, 95: e28727

125 Dang A T, Marsland B J. Microbes, metabolites, and the gut–lung axis. Mucosal Immunol, 2019, 12: 843–850

126 d'Ettorre G, Ceccarelli G, Marazzato M, et al. Challenges in the management of SARS-CoV2 infection: the role of oral bacteriotherapy as complementary therapeutic strategy to avoid the progression of COVID-19. Front Med, 2020, 7: 389

127 Tuvim M J, Evans S E, Clement C G, et al. Augmented lung inflammation protects against influenza A pneumonia. PLoS One, 2009, 4: e4176

128 Yeo J M, Lee H J, Kim J W, et al. *Lactobacillus fermentum* CJL-112 protects mice against influenza virus infection by activating T-helper 1 and eliciting a protective immune response. Int Immunopharmacol, 2014, 18: 50–54

129 De Boeck I, Spacova I, Vanderveken O M, et al. Lactic acid bacteria as probiotics for the nose? Microb Biotechnol, 2021, 14: 859–869

130 De Boeck I, van den Broek M F L, Allonsius C N, et al. *Lactobacilli* have a niche in the human nose. Cell Rep, 2020, 31: 107674

131 Endam L M, Alromaih S, Gonzalez E, et al. Intranasal application of *Lactococcus lactis* W136 is safe in chronic rhinosinusitis patients with previous sinus surgery. Front Cell Infect Microbiol, 2020, 10: 440

132 Montassier E, Kitsios G D, Radder J E, et al. Robust airway microbiome signatures in acute respiratory failure and hospital-acquired pneumonia. Nat Med, 2023, 29: 2793–2804

133 Wang K, Zhang Z, Hang J, et al. Microbial-host-isozyme analyses reveal microbial DPP4 as a potential antidiabetic target. Science, 2023, 381: eadd5787

134 Ke S, Weiss S T, Liu Y Y. Dissecting the role of the human microbiome in COVID-19 via metagenome-assembled genomes. Nat Commun, 2022, 13: 5235

135 Steed A L, Christophi G P, Kaiko G E, et al. The microbial metabolite desaminotyrosine protects from influenza through type I interferon. Science, 2017, 357: 498–502

136 Trompette A, Gollwitzer E S, Pattaroni C, et al. Dietary fiber confers protection against Flu by shaping Ly6c−patrolling monocyte hematopoiesis and $CD8^+$ Tolism. Immunity, 2018, 48: 992–1005.e8

137 Shi C, Zhu H, Li H, et al. Regulating the balance of Th17/Treg cells in gut-lung axis contributed to the therapeutic effect of *Houttuynia cordata* polysaccharides on H1N1-induced acute lung injury. Int J Biol Macromol, 2020, 158: 52–66

138 Hosang L, Canals R C, van der Flier F J, et al. The lung microbiome regulates brain autoimmunity. Nature, 2022, 603: 138–144

139 Wang H, Blackall M, Sominsky L, et al. Increased hypothalamic microglial activation after viral-induced pneumococcal lung infection is associated with excess serum amyloid A production. J Neuroinflamm, 2018, 15: 200

Summary for “呼吸道微生物组与呼吸道感染”

Respiratory microbiome and respiratory infections

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In recent years, the role of the respiratory microbiomes involved in respiratory infections has garnered significant attention. The respiratory tract, which serves as one of the primary interfaces between the internal human body and the external environment, accommodates a diverse microbiome, including bacteria, viruses, fungi, and other microorganisms. The advance of next-generation sequencing technologies has significantly deepened our understanding of the respiratory microbiome, highlighting its critical role in respiratory infections. The microbial composition varies across different regions of the respiratory tract, including the nasal cavity, nasopharynx, oropharynx, and lower respiratory tract. Normally, commensal bacteria in the respiratory tract maintain homeostasis by occupying ecological niches and by promoting colonization resistance to pathogens. Maintaining this healthy microbiome is essential for respiratory health, while microbiome dysbiosis, or disruptions to this balance, has been linked to impaired respiratory function, increased risk of infections, and the exacerbation of pre-existing disorders. The immune state of the lungs is closely connected to the lung microbiome; moreover, the microbiome can influence the lung’s immune response. Respiratory infections can disrupt this microbe-immune balance, leading to inflammation, bacterial movement, and increased viral attachment and replication, all of which can worsen disease outcomes. Depending on the type of infection, this dysbiosis can lead to decreased microbial diversity and specific microbial alterations. In addition to pathogenic bacteria, commensal microbes that are traditionally considered non-pathogenic can sometimes contribute to the development of bacterial pneumonia. Infections caused by other pathogens also induce significant microbiome changes, which are closely linked to infection severity and treatment outcomes. The respiratory microbiome shows great promise as a diagnostic and predictive tool for respiratory illnesses such as acute respiratory distress syndrome (ARDS) and hospital-acquired pneumonia. Regarding critically ill patients, the composition of the pulmonary microbiome can be used to predict clinical outcomes, patient survival rates and the duration of mechanical ventilation needed. This review summarises the current understanding of the distribution of the respiratory microbiome, its alterations during infections, and its clinical consequences. Future research should focus on longitudinal studies to better understand the dynamic changes that occur in the respiratory microbiome during infections, and the mechanisms behind host-microbiome interactions and how they affect immune responses. This review provides new insights to understand the pathogenesis of respiratory infections and enlighten the development of new treatment strategies.

respiratory microbiome, respiratory infections, dysbiosis, immune interaction

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