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人类呼吸道病毒组与疾病发生、免疫发育的范围综述：证据总结与未来方向

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摘　要

目的：系统分析人类呼吸道病毒组相关研究，总结呼吸道病毒组与疾病发生及免疫发育关联的现有证据，为未来该领域研究内容与方向提供依据。方法：遵循范围综述方法框架，系统检索Cochrane Library、PubMed、Embase、Web of Science、中国生物医学文献数据库(CBM)、万方数据库及中国知网(CNKI) 7个中英文数据库，检索时限为2004年1月1日至2025年10月31日。对纳入文献进行归类与描述性分析。结果：共纳入64篇文献，涵盖原始研究与综述，研究地域分布于25个国家和地区，研究对象包括疾病状态人群、健康人群及两者兼有的人群。现有研究多将呼吸道病毒组作为微生物组的次要组分，缺乏对病毒组本身，尤其是共生病毒与宿主免疫发育因果机制的深入探讨。结论：呼吸道病毒组在健康与疾病状态下构成差异显著，且与细菌组、宿主免疫存在复杂交互，但目前针对性研究仍较分散。未来研究应进一步聚焦呼吸道病毒组的功能解析、机制验证及转化应用，推动其从微生物组学的“附属角色”转向独立、系统的研究方向。

关键词

病毒组，病毒基因组，呼吸道疾病，共生病毒，微生物组

Human Respiratory Virome: Associations with Disease Pathogenesis and Immune Development—Evidence Synthesis and Future Directions, a Scoping Review

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Abstract

Objective: To systematically analyze studies on the human respiratory virome, summarize the available evidence linking the respiratory virome to disease pathogenesis and immune development, and provide a basis for future research content and directions in this field. Methods: Following the framework of a scoping review, we systematically searched seven Chinese and English databases: Cochrane Library, PubMed, Embase, Web of Science, Chinese Biomedical Literature Database (CBM), Wanfang Database, and China National Knowledge Infrastructure (CNKI). The search period was from January 1, 2004, to October 31, 2025. The included literature was classified and descriptively analyzed. Results: A total of 64 articles were included, covering original studies and reviews. The studies were conducted in 25 countries and regions, with participants including diseased populations, healthy individuals, and mixed populations. Most existing studies regarded the respiratory virome as a secondary component of the microbiome, lacking in-depth exploration of the virome itself, especially the causal mechanisms between commensal viruses and host immune development. Conclusions: The composition of the respiratory virome differs significantly between healthy and diseased states, and it has complex interactions with the bacteriome and host immunity. However, current targeted studies remain fragmented. Future research should further focus on the functional characterization, mechanistic validation, and translational application of the respiratory virome, promoting its shift from an "auxiliary role" in microbiomics to an independent and systematic research direction.

Keywords

Virome, Viral Genome, Respiratory Diseases, Commensal Viruses, Microbiome

1. 前言

人体微生物组是栖息于不同解剖部位的微生物群落集合，涵盖细菌、真菌、古菌及病毒四大类，共同构成复杂的人体微生物生态系统[1]。作为微生物组的重要组成部分，病毒组包括感染人类细胞的真核病毒、以细菌或古菌为宿主的原核病毒，以及整合于宿主基因组的反转录病毒元件[2]。从宿主关系视角，病毒组成员呈现多样化的生存状态：与宿主长期共存的共生病毒、具有明确致病性的致病病毒，以及仅在宿主免疫或微生物环境改变时表现致病性的机会性病毒[3]。

人类呼吸道作为人体第二大屏障器官，承载着丰富的共生微生物多样性；其中，呼吸道病毒组与机体免疫功能发育及疾病发生密切相关[1]。呼吸道病毒组由真核病毒、噬菌体及部分致病性未知的病毒构成，广泛分布于鼻腔及肺内，在儿童与成人的痰液、鼻咽拭子、口咽拭子及支气管肺泡灌洗液中均可检测出 DNA 病毒、RNA 病毒及噬菌体[4] [5]。

然而，受物理及生物屏障限制，呼吸道病毒组的物种丰富度显著低于肠道等其他病毒组[6]。当前相关研究多附属于细菌组学分析，呈现分散且缺乏系统整合的状态；在研究设计、基因组特征解析及结果解释层面存在较大差异，导致结论一致性不足，尚未形成公认的参考框架。现有研究虽初步探索了疾病状态下呼吸道病毒组的构成变化及其与疾病进展的关联，但关于呼吸道病毒组如何调控宿主免疫发育、参与疾病发生机制等核心问题，仍存在显著的知识空白。

基于上述研究背景，本范围综述旨在系统梳理人类呼吸道病毒组研究现状，整合疾病发生与免疫发育相关的现有证据，识别研究设计的异质性、技术方法的局限及主要知识缺口，从而为未来呼吸道病毒组研究的内容设计与方向选择提供理论依据。系统解析呼吸道病毒组对宿主健康与疾病的作用机制，不仅有助于深化呼吸道微生态学理论，亦为呼吸道感染及相关免疫性疾病的防治策略提供新视角。

2. 方法

2.1. 研究问题

① 人类呼吸道病毒组的组成；
② 呼吸道病毒组在疾病发生发展中的作用；
③ 共生病毒对免疫系统的影响；
④ 呼吸道病毒组与微生物组的关系。

2.2. 研究/检索策略

本研究检索了 Cochrane library、PubMed、Embase、Web of Science、中国生物医学文献数据库(CBM)、万方数据库和中国知网(CNKI)等国内外数据库，采用 MeSH 主题词，自由词及布尔逻辑运算符链接词组合的方式进行检索。英文检索词包括：“virome*”，“viromic*”，“viral genome*”，“virus genome*”，“viral metagenom*”，“virus metagenom*”，“human”，“respiratory disease*”，中文检索词包括：病毒组，病毒基因组，病毒基因组，病毒宏基因组，病毒宏基因组，人类，呼吸道疾病。检索时限为 2000 年 1 月 1 日至 2024 年 12 月 31 日。

2.3. 纳入/排除标准

纳入标准：
① 人群：健康人群或患有呼吸道疾病的人，不分年龄。
② 概念：所有与人类病毒组和呼吸道疾病相关的研究都将包括在内。
a) 呼吸道健康人群(成人和儿童)病毒组组成的研究；
b) 报告人类病毒组与特定呼吸道疾病(成人和儿童)之间关系的研究；
c) 调查常驻/共生病毒对人体影响的研究。
③ 背景：来自任何国家的研究。来自任何医疗保健机构的研究。来自社区、门诊或住院调查的研究。
④ 研究类型：所有类型的研究：文章、综述、病例报告、指南等。
排除标准：
① 研究对象非人类的文献；② 无法获取全文的文献；③ 重复的文献；④ 非中英文文献。

2.4. 文献筛选及数据提取

将文献导入 Endnote 软件去重，由 2 名研究者独立对所得文献进行筛选，提取资料信息进行交叉核对，依据纳入和排除标准，独立阅读题目、摘要进行初筛，并进一步阅读全文进行再次筛选，确定纳入

文献；对于出现分歧的文献由第 3 名研究者讨论后决定是否纳入。纳入后的文章采用数据提取表格提取文章与呼吸道病毒组学研究相关内容，包括文献编号、研究类型、作者、国家、发表年份、健康/疾病、研究人群、研究方法、研究目的、重要研究结论等方面，在此基础上进行描述性研究，研究者均接受专业培训。

3. 结果

3.1. 纳入研究基本信息

通过数据库检索共获得 7327 篇潜在文献，经去重及标题筛选后保留 651 篇摘要，全文评估后纳入 64 篇文献。文献筛选流程如图 1 所示。纳入研究发表于 2003~2025 年，研究地点覆盖 25 个国家和地区。其中，综述类文献 22 篇(34.4%)，原始研究 42 篇(65.6%)。从地域分布来看，欧洲占比最高(n = 22, 34.4%)，其次为亚太地区(n = 17, 26.6%)，北美 11 篇(17.2%)，其他地区 12 篇(18.8%)；另有 1 项为中国与美国合作研究[7]，1 项覆盖欧洲 5 个主要气候区[8]。

研究人群方面，以疾病状态人群为主要对象的研究占主导(n = 51, 79.7%)，8 篇(12.5%)研究仅以健康人群为对象，5 篇(7.8%)研究同时纳入疾病状态与健康人群。年龄分布方面，以儿童为对象的研究 19 篇(29.7%)，以成人为对象的研究 10 篇(15.6%)，同时纳入成人与儿童的研究 7 篇(10.9%)，另有 27 篇未明确提及研究对象年龄(42.2%)。

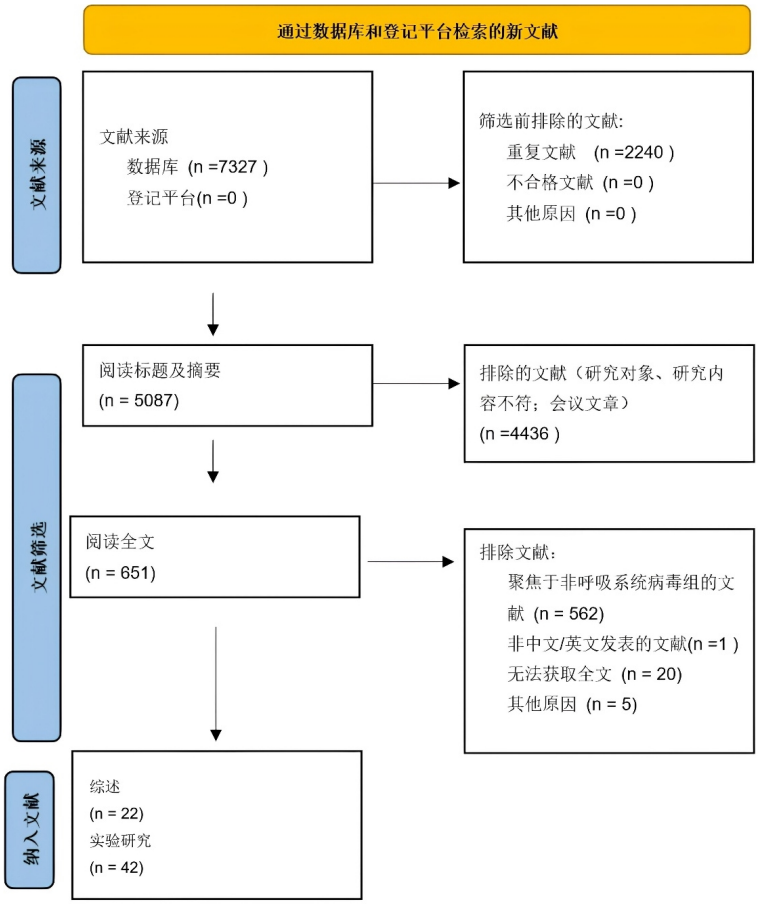

Figure 1. Literature screening flowchart
图 1. 文献筛选流程图

3.2. 人类呼吸道病毒组的组成

“健康病毒组”是相对概念，因难以确证任何病毒在所有条件下均不致病[9]。当前认知主要源自无症状或健康个体的研究[3] [10]-[12]，其组成包括真核呼吸道病毒、非呼吸道真核病毒及噬菌体，这一固有病毒群落被认为参与宿主免疫塑造，并可能调节疾病易感性[3]。

指环病毒(Anelloviruses, AVs)包括细环病毒(TTV)等，于 1997 年首次发现，致病性迄今未明，是健康呼吸道样本中常为真核 DNA 病毒中最主要成分[13] [14]。噬菌体同样稳定检出，其种类、多样性与丰度反映肺部细菌组成，已鉴定科包括微病毒科(Microviridae)、肌尾病毒科(Myoviridae)、短尾病毒科(Podoviridae)和长尾病毒科(Siphoviridae) [11] [15] [16]，宿主涵盖肠杆菌(Enterobacteria)、假单胞菌(Pseudomonas)、克雷伯菌(Klebsiella)、链球菌(Streptococcus)、嗜血杆菌(Haemophilus)等[11] [15] [16] Guo 等(2022)、Li 等(2019)、Sandybayev 等(2024)。人鼻病毒、腺病毒、冠状病毒、流感病毒、呼吸道合胞病毒、人博卡病毒等致病性病毒科，以及乳头瘤病毒科、多瘤病毒科、疱疹病毒科等 DNA 病毒，均在健康儿童与成人的鼻咽部被检出[10]-[12] [17]。上述发现提示健康呼吸道病毒组兼具共生与潜在致病病毒，其功能作用及对呼吸道稳态的贡献仍需进一步研究。

3.3. 呼吸道疾病状态下的病毒组构成

宏基因组测序分析显示，呼吸系统疾病人群的病毒组多样性低于健康对照组，提示疾病相关病毒组构成改变[18] [19]。本节将探讨四种不同疾病下呼吸道病毒组研究的最新证据。

3.3.1. 哮喘

真核病毒是哮喘急性发作的重要诱因，尤以人鼻病毒、呼吸道合胞病毒为主[20] [21]。急性期病毒组主要由副粘病毒科、小核糖核酸病毒科、弹状病毒科、衣原病毒科、正粘病毒科及疱疹病毒科构成[22]。哮喘患者气道病毒组与健康对照组存在显著差异：哮喘组疱疹病毒占比最高(44.6% ± 4.6%)，其中巨细胞病毒与 EB 病毒分别为 24.5% ± 3.3%和 16.9% ± 3.5%，而健康对照组仅 5.4% ± 2.5%和 7.1% ± 3.0% [23]。稳定期成人哮喘痰液中，噬菌体丰度降低、疱疹病毒科(巨细胞病毒、EB 病毒)增加与病情严重程度及恶化风险相关[23]；儿童哮喘则表现为噬菌体多样性与丰度降低，指环病毒(AVs)及呼吸道合胞病毒检出率升高[24]。

3.3.2. 呼吸道感染

呼吸道感染的临床定义及标本类型(鼻咽拭子、痰液、肺泡灌洗液等)存在异质性，限制了研究结论的一致性[15] [16] [25]-[28]。儿童急性呼吸道感染中，呼吸道合胞病毒、人鼻病毒检出率最高[29] [30]，人冠状病毒、细环病毒、人博卡病毒、副流感病毒、流感病毒及腺病毒亦可检出(载量 0.01%~24.3%) [31]。慢性下呼吸道感染中，鼻病毒最为常见，EB 病毒(31%)、疱疹病毒(29%)、腺病毒(18%)亦有检出[32] [33]。鼻窦炎患者可检出偏肺病毒、鼻病毒[34] [35]。哮喘患者呼吸道病毒以鼻病毒为主[24] [36]，同时可检出呼吸道合胞病毒及博卡病毒[22]。与健康对照相比，急性感染期致病性真核病毒多样性与丰度升高，而 AVs 丰度保持稳定[10] [12] [16]，重症感染中甚至更高[37]，提示共生病毒与疾病严重程度存在潜在关联。

3.3.3. 肺囊性纤维化(CF)

CF 患者气道中鼻病毒最常见，流感病毒及呼吸道合胞病毒临床影响最显著[38] [39]；儿童微生物组多样性高于成人[40]。与非 CF 患者相比，CF 患者真核病毒组呈高度多变特征，疱疹病毒科、逆转录病毒科等可占主导；噬菌体群落相应反映定植病原体(假单胞菌、伯克霍尔德菌、肠杆菌、链球菌等)，而非 CF 样本噬菌体群体相对稳定。CF 痰液中尚可检出 AVs、腺病毒科、乳头瘤病毒科等真核 DNA 病毒[40]-

[42]。

3.3.4. 慢性阻塞性肺疾病(COPD)

COPD 急性加重期可检出流感病毒、鼻病毒、呼吸道合胞病毒、副流感病毒、人冠状病毒、人博卡病毒、腺病毒，以鼻病毒最常见，其次为呼吸道合胞病毒及流感病毒[43] [44]。COPD 患者肺泡灌洗液及痰液病毒组富含噬菌体群落及 DNA 病毒(AVs、逆转录病毒科、疱疹病毒科)，其多样性随疾病严重程度增加而降低[45]。

3.4. 呼吸道病毒组在疾病发生发展中的作用

健康与疾病状态下呼吸道病毒组的构成存在显著差异。既往观点认为细菌感染是呼吸道疾病加重的主要诱因，但随着 PCR 技术的普及，病毒感染也被确认为关键驱动因素，其中人鼻病毒(HRV)和呼吸道合胞病毒(RSV)与慢性气道炎症性疾病的发生及恶化关联最为密切[46] [47]。

呼吸道病毒主要感染并复制于气道上皮细胞[48]。复制过程中，细胞释放抗病毒因子及细胞因子，改变局部炎症状态与气道微生态[49]。健康气道中，病毒感染诱导 I 型炎症反应，激活抗病毒状态并募集效应细胞，最终炎症消退、病毒清除[50] [51]。在慢性炎症状态下，抗病毒应答受损或失调，导致炎症持续、免疫细胞异常浸润及症状加重[49]。慢性气道炎症患者对呼吸道病毒的易感性增高，急性加重频率随之上升，形成恶性循环[49] [52] [53]。

肺炎患儿 TTV 载量显著高于轻症患儿[54]；TTV 负荷与外周气道气流受限、支气管扩张严重程度及肺功能下降呈显著正相关[55]。TTV 或与流感样症状相关，但其致病性及在健康个体中长期携带的机制尚待阐明。急性呼吸道感染儿童中，病毒组家族多样性及序列丰度均高于未感染组[56]；Wylie 等报告发热儿童鼻咽拭子病毒序列高于无发热儿童，Wang 等报道急性呼吸道感染儿童病毒载量亦高于非急性感染儿童[12] [31]。

K. F. Budden 等指出，生命早期病毒感染是哮喘发生的潜在关键触发因素[57]。学龄前哮喘儿童在无症状期即呈现与健康儿童显著差异的病毒组特征：噬菌体丰度及多样性降低，真核病毒丰度升高，提示原有微生物群落抗病毒屏障减弱[24]。病毒检出并非总与感冒或哮喘症状同步，但病毒感染与哮喘症状严重程度呈正相关，病毒性疾病较非病毒性疾病症状更重、病程更长、哮喘控制更差。学龄儿童中约 80%的哮喘急性发作、成人中约 50%与病毒感染相关，以鼻病毒、呼吸道合胞病毒及其他社区获得性病毒为主[7]。上述证据表明，病毒感染是重症感冒及哮喘恶化的密切关联因素，病毒与非病毒因素协同作用可能是产生显著症状的必要条件[36] [58]。

3.5. 共生病毒对免疫系统的影响

AVs 于生命早期获得，经粪－口或呼吸道途径建立持续性感染，通常不引发显性疾病。其复制水平受宿主免疫活性负向调控：免疫抑制状态(如 HIV 感染、肺移植术后)下 AVs 载量显著升高[58]。AVs 可激活先天免疫系统炎症小体，在宿主防御多种病原体中发挥重要作用；移植患儿低 AVs 基因组拷贝数与移植排斥或死亡风险增加相关[59]。AVs 在哺乳动物中普遍持续存在，构成人类病毒组的重要组分，是理解病毒－宿主共生关系及免疫塑造功能的理想模型[60]。TTV 作为 AVs 代表成员，虽在人群中流行率极高，但其与宿主的精确互作模式及在特定疾病中的病因学角色仍未阐明。

BARR 等人表明，噬菌体结合气道粘蛋白并减少细菌定植，支持了其在肺部潜在的屏障保护作用[61]。相反，一些噬菌体可能会负面调节宿主免疫力；例如，由铜绿假单胞菌产生的丝状 Pf 噬菌体在鼠类和体外模型中显示，通过 Toll 样受体 3 介导的 I 型干扰素信号传导抑制抗菌反应，损害吞噬作用并促进慢性感染。这些 contrasting 的作用突出了在 ARI 中探索噬菌体功能(而不仅仅是组成)的必要性[62]。

3.6. 呼吸道病毒组与细菌组的关系

慢性气道炎症性疾病的发生常伴随特定致病菌在炎症气道中的优势扩增[63]。病毒感染——尤其是人鼻病毒感染——可通过多重机制扰动呼吸道细菌群落：一方面直接破坏上呼吸道生物被膜，促使肺炎链球菌等条件致病菌释放并播散至下呼吸道，加重局部炎症[64] [65]；另一方面通过改变气道微环境营养成分，选择性促进特定细菌生长[66] [67]。此外，病毒感染本身可损害宿主对细菌的免疫应答，而皮质激素等抗炎药物在控制症状的同时进一步削弱局部免疫防御功能，为机会性病原体取代正常共生菌群创造条件，推动菌群结构失调及炎症特征的持续改变[68]-[72]。

上述病毒–细菌交互作用形成恶性正反馈：病毒感染触发菌群失调与致病菌扩增，致病菌负荷增加进一步加重气道炎症，并提高对后续病毒感染的易感性，最终表现为更严重、更频繁的急性加重[69] [73]。基于微生物组的治疗策略虽尚处起步阶段，但在肠易激综合征等肠道疾病中已通过恢复菌群生态显示出临床疗效[74]。类似思路为呼吸道病毒组–细菌组交互失衡的靶向干预提供了重要启示，未来研究应聚焦于气道特异性菌群调节手段，以修复病毒感染后受损的微生物生态系统。

4. 讨论

本范围综述系统梳理了人类呼吸道病毒组在健康与疾病状态下的构成特征、功能关联及研究进展，结果显示：健康人群呼吸道病毒组以 AVs 等共生真核病毒及多样化的噬菌体群落为稳定组分。共生病毒亦常见于血液、皮肤及肠道等其他器官系统，提示其可能作为人体跨器官病毒组核心成员的潜在角色。在疾病状态下，呼吸道病毒组呈现显著的构成重塑：人鼻病毒、呼吸道合胞病毒及流感病毒等致病性真核病毒丰度升高，噬菌体多样性与丰度普遍下降，且不同疾病——如哮喘、COPD、CF 及急性呼吸道感染——表现出各异的病毒组多样性偏移模式。上述发现提示呼吸道病毒组并非被动伴随的微生物集合，而是主动参与宿主免疫塑造、菌群交互及疾病发生发展的功能性生态网络。

呼吸道病毒对疾病进程的影响涉及多重机制，其中对宿主免疫功能的影响及对其他微生物组(尤其是细菌组)的调节是两条核心路径。病毒感染可直接诱导气道上皮炎症应答，在慢性炎症背景下演变为持续免疫激活与组织损伤；同时，病毒可通过破坏生物被膜、改变微环境营养构成、削弱抗菌免疫应答等途径扰动细菌群落稳态，形成病毒–细菌协同致病环路，加剧急性加重频率与严重程度。然而，尽管病毒–细菌共感染及其临床意义已被广泛报道，目前对呼吸道病毒组，尤其是共生病毒与噬菌体，在维持呼吸道稳态、调控细菌定植抗性及训练黏膜免疫中的基础性功能，认知仍极为有限。

近年来呼吸道微生物组研究取得了长足进展，但多数研究仍以细菌组为核心，病毒组往往作为附属分析对象，或受限于方法学瓶颈而未被充分解析。本综述所纳入文献中，专门以呼吸道病毒组为主要研究目标的原始研究不足半数，且研究设计、样本类型、测序策略及生物信息分析流程高度异质，限制了跨研究比较与结论整合。更重要的是，当前研究多停留于病毒组构成与疾病状态的关联描述，难以确证因果关系。病毒载量变化是疾病恶化的原因还是结果、共生病毒丰度波动是免疫稳态失衡的标志抑或代偿保护机制等核心问题，仍缺乏纵向干预及机制验证研究支撑。

然而，人类呼吸道病毒对健康与疾病的影响可能不亚于细菌组。噬菌体作为细菌宿主的专性寄生物，其群落动态直接影响细菌种群结构、毒力基因水平转移及代谢功能输出；在肺囊性纤维化及 COPD 等疾病中，噬菌体组成与致病菌定植谱高度对应，提示其既可作为菌群状态的指示标志，亦具备内源性抗菌调控的潜在功能。AVs 等共生真核病毒与宿主免疫活性呈负相关，在免疫抑制个体中显著扩增，其低载量与移植患儿不良预后相关——这一模式强烈提示共生病毒与宿主免疫系统之间存在精细的共调关系，可能是“健康病毒组”定义的核心维度之一。

当前，以宿主核酸去除、宏基因组测序及病毒组富集技术(Viral enrichment)为代表的方法学突破，为

突破呼吸道病毒组研究瓶颈提供了新的技术窗口[75]-[77]。这些方法显著提升了低生物量样本中病毒序列的检出灵敏度与覆盖广度，使纵向追踪健康人群病毒组动态、系统解析噬菌体–细菌互作网络、以及挖掘共生病毒免疫调控功能成为可能。未来研究应着力于以下方向：一、建立健康人群呼吸道病毒组参考图谱，明确核心病毒成员、时序稳定性及个体间变异度；二、整合宏基因组、宏转录组及代谢组等多组学手段，从功能基因表达、宿主应答特征及代谢输出层面揭示病毒组与疾病因果关联；三、将病毒组纳入呼吸道微生物组–宿主–环境交互框架，以系统生物学视角解析呼吸道疾病的多重驱动因素；四、探索基于病毒组调控的干预策略，如靶向噬菌体组以重塑菌群生态，或利用共生病毒的免疫调节特性构建新型生物治疗载体。

总之，呼吸道病毒组不再是微生物组学中被忽视的“暗物质”，而是理解呼吸道健康与疾病不可或缺的功能维度。从描述病毒“有或无”迈向解析病毒“如何作用”，从单一病毒致病论转向病毒组–细菌组–宿主三元互作范式，呼吸道病毒组研究正处在这一范式转型的关键节点。本综述所揭示的证据基础与知识缺口，为后续研究明确了起点与方向。

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