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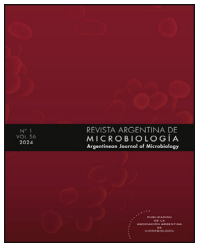

EDITORIAL

The respiratory microbiota: From passive spectator to active guardian of lung immunity

La microbiota respiratoria, de espectadora pasiva a guardiana activa de la inmunidad pulmonar

For decades, the lower respiratory tract was considered a sterile environment, with microbes viewed almost exclusively as agents of infection. Advances in culture-independent sequencing technologies have fundamentally challenged this paradigm, revealing that the respiratory tract hosts dynamic and structured microbial communities that contribute to immune homeostasis, disease susceptibility, and clinical outcomes[1–3]. These discoveries have reshaped our understanding of respiratory health and positioned the respiratory microbiota as an active biological determinant rather than a passive component of the respiratory system.

The respiratory tract represents a complex ecological continuum extending from the nasal cavity to the pulmonary alveoli. While microbial biomass decreases from the upper to the lower airways, microbial diversity and composition remain remarkably interconnected. In healthy individuals, the lung microbiota closely resembles that of the upper respiratory tract, reflecting a dynamic balance between microbial immigration – driven by inhalation, microaspiration, and mucosal dispersion – and elimination through mucociliary clearance and innate immune mechanisms[1–3]. This ecological equilibrium is highly sensitive to host physiology and environmental exposure. Factors such as oxygen tension, temperature, humidity, mucus production, and nutrient availability shape niche-specific microbial communities. Importantly, health is associated with microbial diversity and stability, whereas disease states frequently correlate with reduced diversity and the expansion of pathobiont or pathogenic taxa.

Beyond their ecological presence, respiratory commensal bacteria exert profound effects on mucosal immunity. Experimental models have demonstrated that the absence or disruption of the respiratory microbiota leads to exaggerated inflammatory responses, impaired immune regulation, and increased susceptibility to infections[4]. These findings highlight a fundamental role for commensal microorganisms in calibrating immune thresholds within the lung. Mechanistically, respiratory bacteria interact with epithelial cells, dendritic cells, and alveolar macrophages, influencing cytokine production, antimicrobial peptide expression, and antigen presentation. These interactions promote immune tolerance under homeostatic conditions while preserving the capacity for rapid and effective responses to pathogens. Thus, the respiratory microbiota functions as a critical regulator of immune balance, preventing both impairments of defenses and excessive inflammation[4].

Thus, the establishment of the respiratory microbiota during early life represents a critical window for immune programming. Mode of delivery, feeding practices, antibiotic exposure, and early respiratory infections significantly influence microbial succession in the airways[2]. Vaginal delivery and breastfeeding favor the early colonization by beneficial commensals such as *Corynebacterium* spp. and *Dolosigranulum* spp., which have been consistently associated with reduced respiratory infections and improved immune outcomes[2–4]. Disruptions during this developmental window can have lasting consequences. Premature or aberrant microbial transitions – such as early dominance of *Moraxella* spp. or *Streptococcus* spp. – have been linked to increased susceptibility to respiratory infections, wheezing disorders, and asthma later in life[2,3]. These observations support the concept that respiratory microbiota maturation is not merely descriptive but causally related to long-term respiratory health.

Respiratory infections represent one of the clearest contexts in which the protective role of the microbiota becomes evident. Commensal bacteria can inhibit pathogen colonization through competitive exclusion, nutrient depletion, and the production of antimicrobial compounds[4]. Moreover, they modulate host immunity, enhancing antiviral and antibacterial defenses while limiting tissue damage. Experimental

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evidence indicates that specific respiratory commensals can reduce pathogen burden, attenuate lung injury, and improve survival following viral and bacterial challenges, highlighting the necessity of precise microbial selection for therapeutic applications[4].

The recognition that respiratory commensal bacteria actively shape lung immunity has opened new avenues for translational research. Selected strains of human respiratory commensal bacteria belonging to *Corynebacterium* spp., *Dolosigranulum* spp., and *Lacticaseibacillus* spp. have demonstrated the capacity to enhance innate and adaptive immune responses, promote regulatory pathways, and protect against diverse respiratory pathogens in preclinical models[4,5]. These findings challenge the traditional gut-centric view of probiotic intervention to modulate the gut-lung axis and support the emergence of ''respiratory probiotics'' as next-generation immunomodulatory tools. Unlike conventional probiotics, which primarily target intestinal health, respiratory commensals are uniquely adapted to interact with airway epithelia and lung immune cells, offering targeted benefits for respiratory diseases. Notably, not all respiratory commensals confer protection. Beneficial effects are strictly strain-specific, emphasizing the importance of rigorous functional screening rather than taxonomic classification alone[4,5]. As an example, it was demonstrated in mice models that nasal administration of the human respiratory commensal *Corynebacterium pseudodiphtheriticum* 090104 beneficially modulates respiratory innate immunity and enhances host resistance to respiratory infections caused by the respiratory syncytial virus, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae*. Nasal treatment with strain 090104 significantly reduced pathogen replication and lung tissue damage, and this protective effect was associated with enhanced activation of alveolar macrophages and the induction of balanced Th1 ($CD4^+IFN\text{-}\gamma^+$) and regulatory T cell ($CD4^+IL\text{-}10^+$) responses in the respiratory tract[4,5]. Of note, the immunomodulatory effect of *C. pseudodiphtheriticum* 090104 was not achieved by several other strains of the same species.

Despite rapid progress in the characterization of respiratory commensals as potential ''next-generation probiotics'' for the respiratory tract, key challenges remain. Causal relationships between microbiota alterations and disease must be firmly established through longitudinal and interventional studies. Additionally, standardized methodologies for sampling, analysis, and functional validation are needed to harmonize findings across studies. From a translational perspective, safety, stability, and regulatory considerations will shape the development of respiratory microbiota-based interventions. In this context, rigorous safety evaluation is essential, as respiratory commensal bacteria differ fundamentally from conventional intestinal probiotics. While most intestinal probiotics consist of lactobacilli and bifidobacteria with a long history of safe use, respiratory commensal species have only recently emerged as candidates for therapeutic application and therefore require comprehensive safety assessment prior to clinical or field implementation.

The respiratory microbiota has emerged as a central player in lung immunity, influencing susceptibility to infection, chronic inflammation, and immune maturation across the lifespan. Moving beyond descriptive studies toward mechanistic and translational research will be essential to harness its full potential. As our understanding deepens, respiratory commensal bacteria may become integral components of innovative strategies aimed at preserving and restoring respiratory health in both clinical and public health contexts.

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