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The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases

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Abstract

The pulmonary microbial community, described only a few years ago, forms a discreet part of the human host microbiota. The airway microbiota has been found to be substantially altered in the context of numerous respiratory disorders; nonetheless, its role in health and disease is as yet only poorly understood. Another important parameter to consider is the gut–lung axis, where distal (gut) immune modulation during respiratory disease is mediated by the gut microbiota. The use of specific microbiota strains, termed “probiotics,” with beneficial effects on the host immunity and/or against pathogens, has proven successful in the treatment of intestinal disorders and is also showing promise in the context of airway diseases. In this review, we highlight the beneficial role of the body's commensal bacteria during airway infectious diseases, including recent evidence highlighting their local (lung) or distal (gut) contribution in this process.

1 | INTRODUCTION

“Microbiota” refers to the community of microorganisms, including bacteria, viruses, fungi, and protozoans, that live in a host (Limon et al., 2017; Mirzaei et al., 2017). The human body is host to at least as many microbes as there are human cells (Sender et al., 2016), and these microbes are present in all mucosal sites. The beneficial role of our microbiota in shaping the immune system and in maintaining homeostasis has been known for more than a century from studies of the gut, the organ where the microbial population is the more abundant (Brestoff et al., 2013; Lozupone et al., 2012). Studies using germ-free (GF) mice or mice treated with broad-spectrum antibiotics have highlighted the protective role of the host microbiota in a variety of pathological settings, ranging from metabolic disorders (Turnbaugh et al., 2006) to inflammatory and infectious diseases in the gut and at distal body sites, such as the skin and the lungs (Khosravi et al., 2014; Samuelson et al., 2017; Zhang et al., 2015).

The host-microbiota symbiotic equilibrium is highly sensitive to a number of intrinsic and environmental factors, including the host genetic background, the use of antibiotics, diet, the presence of allergens or infectious agents, all of which can disturb microbiota composition, leading to a state of “dysbiosis” (Levy et al., 2017). Dysbiosis

can result in disease aggravation or increased susceptibility to new disorders, such as the growth of potentially pathogenic commensals or pathobionts. The development of metaomics approaches (including 16S ribosomal RNA profiling and the more accurate shotgun-sequencing technology) has allowed a more detailed and extensive definition of the microbiome of healthy subjects throughout life and its dependence on gender, diet, or geographical location, as well as on the body sites sampled (Eckburg et al., 2005; Peterson et al., 2009; Yatsunenko et al., 2012) and its alteration during disease (Ley et al., 2006; Nelson et al., 2012). Metagenomic approaches also revealed the presence, composition, and relative abundance of microbial commensals at body sites previously thought to be sterile, such as the lungs. Such sequencing-based approaches were complemented and confirmed by culture-based approaches (Remot et al., 2017). Since 2010, studies have described alterations of the lung microbiota in a number of disease conditions, such as chronic obstructive pulmonary disease, cystic fibrosis, and asthma (Hilty et al., 2010; Pragman et al., 2012; Willner et al., 2012), indicating that the lung microbiota influences both respiratory health and disease. In addition, the gut microbiota has been shown to influence pulmonary immunity through what is commonly referred to as the gut–lung axis (Budden et al., 2017; Trompette et al., 2014).

This review focuses on respiratory infectious diseases, caused by a broad range of airborne pathogens, causing acute or chronic infections. We highlight the beneficial role of the host commensal bacteria during these pathologies, notably in mouse models of dysbiosis, which involve the gut–lung axis (Table 1). Finally, we discuss strategies aimed at modifying the host microbiota (e.g., using probiotics), especially targeting the lungs as a strategy to combat respiratory infections (Figure 1).

2 | THE LUNG MICROBIOTA IN HEALTH AND DISEASE

The lungs are inhabited by a microbial population distinct from that of the gut (Man et al., 2017). Although the human core gut and lung microbiota are similar at the phylum structure level (e.g., Bacteroidetes and Firmicutes predominate in the gut, and Bacteroidetes, Firmicutes, and Proteobacteria are predominant in the lung), they differ in their bacterial species composition. For example, although *Faecalibacterium prausnitzii* and *Bacteroides thetaiotaomicron* are found in the intestinal tract and not in the lung (Lopez-Siles et al., 2012; Mahowald et al., 2009), *Haemophilus spp.*, *Pseudomonas spp.*, *Streptococcus spp.*, and *Veillonella spp.* are frequently found in the airways and not in the gut (Charlson et al., 2011; Morris et al., 2013). The characterisation of the lung microbiota in humans is complicated by the invasive methods required to sample the lower respiratory tract, making contamination with populations of the upper respiratory tract a serious problem (Dickson et al., 2017). However, in mice, it is possible to directly collect lung tissues aseptically in order to carefully assess their microbial composition. Studies in mice have confirmed that the lung microbiota is variable and different of those from other body sites, such as the oral cavity or the gut (Dickson et al., 2018; Kostic et al., 2018).

Alteration of the lung and gut microbiota has been observed in many respiratory diseases (Dickson et al., 2014; Taylor et al., 2016). Whether microbial dysbiosis at both sites is a cause or a consequence of disease remains to be determined, for example, using the mouse models. However, since the gut microbiota is the largest and most diverse community of the mammalian microbiome, with an important impact on immunity in both the gut and the lungs, the specific contribution of the lung microbiota to the host immunity remains difficult to assess. The intensive present focus on the gut–lung axis overshadows the potential role of local microbiota in health and airway diseases (Dickson et al., 2017).

3 | PROTECTIVE ROLE OF THE HOST MICROBIOTA DURING DISEASES OF THE AIRWAYS: INVOLVEMENT OF LOCAL AND DISTAL COMMUNITIES

3.1 | Acute bacterial infections

The composition of the airway microbiota has been studied extensively in patients with chronic airway diseases of both infectious and non-infectious origins (Marsland et al., 2014). By contrast, analysis of

the composition of this microbial community has been poorly explored in patients suffering from acute lung infections, such as pneumonia, probably due to the short duration of such diseases. However, the beneficial role of the host microbiota during acute bacterial infections of the lungs has been demonstrated in numerous settings using GF mice. For example, GF mice are more sensitive to lung infection by *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae* (Brown et al., 2017; Fagundes et al., 2012; Fox et al., 2012). Dissection of the molecular mechanisms involved in host protection against lung infections by the microbiota has been limited because of the complication that, in addition to profound anatomical and developmental differences compared with specific pathogen-free mice, GF mice display an altered immune system (Al-Asmakh et al., 2015). To avoid this problem, recent studies have used combinations of broad-spectrum antibiotics to provoke dysbiosis and assess the role of the bacterial microbiota in resistance to pulmonary infections in mice (Table 1).

In general, studies using antibiotic-treated mice have not addressed whether oral antibiotic administration also eliminated all or part of the lung microbiota, in addition to gut microbial communities; however, it seems likely that this is the case, because such treatments are known to affect the upper airways community (Cheng et al., 2017). Antibiotic-treated mice have been reported to be more susceptible to respiratory pathogens such as *S. pneumoniae* and *K. pneumoniae*. In particular, antibiotic-treated mice infected with *S. pneumoniae* suffered a defect in lung cytokine production. Faecal transplantation by oral gavage with a normal gut microbiota restored both control of the infection in the mice and cytokines' levels in the lungs, illustrating the contribution the gut microbiota makes to lung immunity (Schuijt et al., 2016). Nevertheless, the potential role of the local, pulmonary microbiota in host defence against *S. pneumoniae* remains to be evaluated (Lankelma et al., 2017). In another study, susceptibility to *S. pneumoniae* and *K. pneumoniae* infection in antibiotic-treated mice correlated with reduced production of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-17A in the lungs (Brown et al., 2017). Control of infection was restored after the transfer of a normal microbiota from the upper respiratory tract (via the intranasal route) or after faecal transplantation (via the oral route), demonstrating a beneficial role of both local and distal microbiota on lung immunity. This beneficial effect was abolished when a GM-CSF-neutralising antibody was delivered intranasally. GM-CSF levels were restored following intranasal administration of IL-17A in antibiotic-treated mice, indicating that the microbiota protects the host from respiratory pathogens via IL-17A, which in turn regulates local GM-CSF production (Brown et al., 2017). Finally, in the context of infection with *K. pneumoniae*, microbiota depletion by oral antibiotic administration prevented the innate immune clearance of this pathogen (Clarke, 2014). Although the oral administration of bacterial nucleotide-binding oligomerization domain (NOD)-like receptor ligands rescued the host's ability to control the infection, intranasal administration of these ligands failed to do so. This study highlights the complexity of the mechanisms employed by the microbiota in the gut–lung axis for sustaining host immunity in the lungs.

In the context of acute infections, it has also been shown that specific commensals have the capacity to regulate host immunity.

TABLE 1 Studies of the impact of the microbiota or probiotics administration on host resistance to pulmonary pathogens

| Mouse model | Pathogen studied | Main findings | Phenotype rescue (route of administration) | References |
|---------------------|--|---|--|-----------------------|
| Germ free | <i>Klebsiella pneumoniae</i> | Survival ↓; CFUs ↑ in blood and lungs; neutrophils, CXCL1, TNFα ↓, and IL-10 ↑ in lungs | IL-10 blocking antibody (s.c.); LPS (i.p.); faecal transplant (i.g.) | Fagundes et al., 2012 |
| | <i>Streptococcus pneumoniae</i> | CFUs ↑ in lungs | High NOD2-stimulating bacteria group (i.g.) | Brown et al., 2017 |
| | <i>Pseudomonas aeruginosa</i> | Survival ↓; TNFα and IL-1β ↓ in BALF; intestinal epithelial apoptosis ↓ | | Fox et al., 2012 |
| | <i>P. aeruginosa</i> | CFUs ↑ in lungs and blood | | Robak et al., 2018 |
| Antibiotics treated | <i>Escherichia coli</i> (pneumonia) | Survival ↓; CFUs ↑ in blood and lungs; NF-κB binding activity, TNFα ↓, and IL-6, IL-1β ↑ in lungs; MPO activity in lungs and killing activity of AM ↓ | LPS (oral, drinking water) | Chen et al., 2011 |
| | <i>K. pneumoniae</i> | CFUs ↑ in lungs; TNFα and IL-6 ↓ in lungs; ROS-mediated killing by AM ↓ | NLR ligands (i.g.); AM (i.n.) | Clarke, 2014 |
| | <i>K. pneumoniae</i> <i>S. pneumoniae</i> | Survival ↓; CFUs ↑ in lungs; GM-CSF, IL-17A, CXCL1, and CXCL2 ↓ in lungs | Faecal transplant (i.g.) and lavage fluid (i.n.); NLR-stimulating bacteria (i.n.); GM-CSF, IL-17A-neutralising antibodies, and GM-CSF, IL-17A recombinant cytokines (i.n.) | Brown et al., 2017 |
| | <i>S. pneumoniae</i> | Survival ↓; CFUs ↑ in blood and lungs; inflammatory and tissues damages ↑ in lungs and gut; IL-10, TNFα ↓, and IL-1, IL-6, CXCL1 ↑ in lungs; phagocytosis and cytokine production by AM ↓ | Faecal transplant (i.g.) | Schuijt et al., 2016 |
| | <i>P. aeruginosa</i> | Survival ↓; CFUs ↑ in lungs, BALF, and blood; IL-6, CXCL2, and neutrophils ↑ in BALF; IgA ↓ in BALF and blood | IgA purified (i.n.) | Robak et al., 2018 |
| | <i>Mycobacterium tuberculosis</i> | Lungs damages and CFUs ↑ in lungs, spleen, and liver; Treg ↑ and Th1 ↓ in spleen | Faecal transplant (i.g.) | Khan et al., 2016 |
| Conventional | Influenza virus | Body weight loss, virus titre, symptoms, and histopathology scores ↓; myeloid cells, NK, IL-1-α/β, IL-33 ↑, and eotaxin, MIP-1, MCP-1, IFNγ ↓ in lungs; IL-10 in lungs ↓ (early response) and ↑ (late response) | <i>Lactobacillus paracasei</i> CNCM I-1518 (i.g.) | Belkacem et al., 2017 |
| | Influenza virus | Body weight loss, histopathology, and viral titre ↓; TNFα, IL-6 ↓, and IL-12, IFNγ ↑ in BALF | <i>Lactobacillus plantarum</i> DK119 (i.g. or i.n.) | Park et al., 2013 |
| | Influenza virus | Survival ↑ (highest protection with <i>Lactobacillus fermentum</i> -1); virus titre and histopathology ↓; IgA ↑ and TNFα and IL-6 ↓ in lungs | eight different lactobacillus strains (i.g. or i.n.) | Youn et al., 2012 |
| | <i>P. aeruginosa</i> | Survival ↑; CFUs and histopathology scores ↓; IL-6 ↓ and IL-10 ↑ in serum and lungs; neutrophils ↓ and Treg ↑ in lungs | <i>Lactobacillus rhamnosus</i> GG (i.g.) | Khailova et al., 2013 |
| | <i>S. pneumoniae</i> | CFUs and histopathology scores ↓; specific IgG and IgA ↑ in BALF; neutrophils, TNFα ↑ (early response), | <i>Lactobacillus casei</i> (i.g.) | Racedo et al., 2006 |

(Continues)

TABLE 1 (Continued)

| Mouse model | Pathogen studied | Main findings | Phenotype rescue (route of administration) | References |
|-------------|------------------------------|---|--|----------------------|
| | | and \downarrow (late response) in serum and lungs; IL-10 \uparrow in serum and lungs | | |
| | <i>K. pneumoniae</i> | Survival \uparrow ; body weight loss, CFUs and histopathology score \downarrow ; TNF α and IL-6 in BALF \downarrow ; IL-10 \uparrow in lungs; ROS and bacterial killing by AM \uparrow | <i>Bifidobacterium longum</i> 5 ^{1A} , live, or heat-killed bacteria (i.g.) | Vieira et al., 2016 |
| | RSV and <i>S. pneumoniae</i> | Body weight loss, viral titre, CFUs, and histopathology score \downarrow ; IFN β , IFN γ , TNF α , IL-6, IL-10 \uparrow in BALF; DC, AM, CD4 T cells \uparrow in lungs | <i>Corynebacterium pseudodiphthericum</i> 090104 (i.n.) | Kanmani et al., 2017 |

Note. AM: alveolar macrophages; BALF: broncho alveolar lavage fluid; CFUs: colony forming units; CXCL: chemokine (C-X-C motif) ligand; DC: dendritic cells; GM-CSF: granulocyte colony stimulating factor; IFN: interferon; Ig: immunoglobulin; IL: interleukin; i.g.: intragastric administration (gavage); i.n.: intranasal administration; i.p.: intraperitoneal administration; LPS: lipopolysaccharide; MCP: monocyte chemoattractant protein; MIP: macrophage inflammatory protein; MPO: myeloperoxidase; NF- κ B: nuclear factor kappa-light chain enhancer of activated B cells; NK: natural killer lymphocytes; NLR: nucleotide-binding domain leucine-rich repeat containing; NOD: NLR, nucleotide oligomerization domain-like receptor ligands; ROS: reactive oxygen species; RSV: respiratory syncytial virus; s.c.: subcutaneous administration; Th: T-helper lymphocyte; TLR: toll like receptor; TNF: tumour necrosis factor; Treg: regulatory T cells.

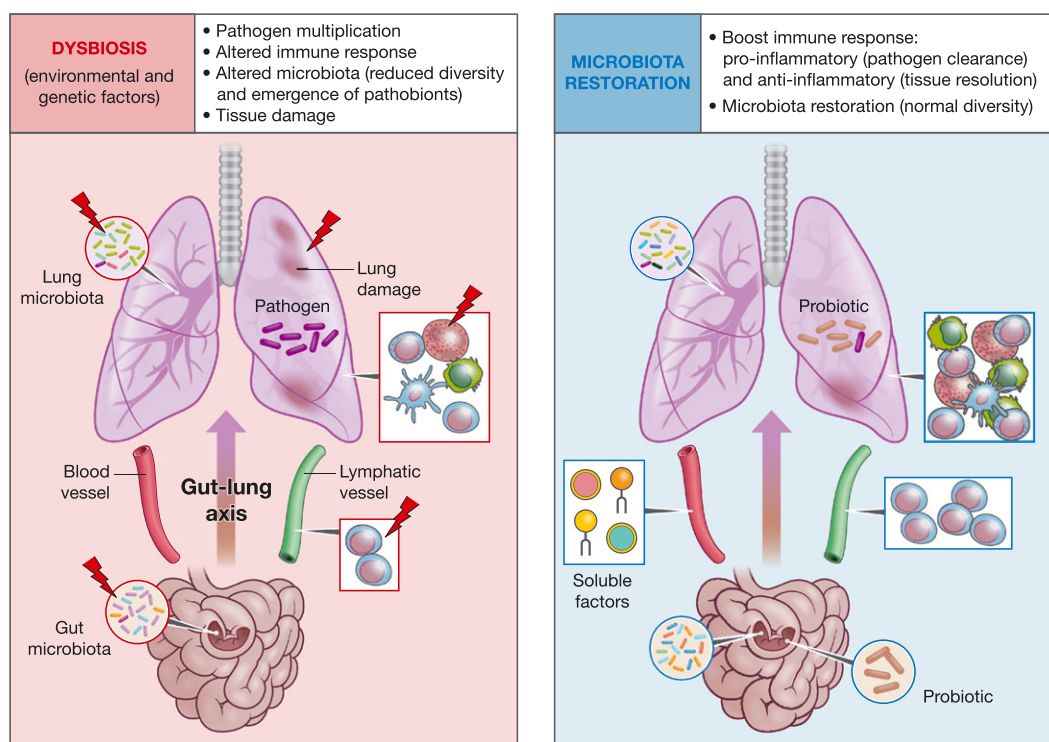


FIGURE 1 Model of the host-microbiota interaction during dysbiosis (and microbiota restoration) within the context of pulmonary infectious disease: the gut-lung axis. The dysbiotic state (i.e., the alteration of the function and composition of the microbiota) can be caused by a variety of environmental (e.g., pathogenic and allergenic contexts and diet) or genetic-induced (e.g., autoimmunity) factors and/or disorders. In this model, a respiratory pathogen causes dysbiosis where the commensal bacterial diversity is perturbed, and pathobionts (i.e., any potentially disease-causing microorganism) can subsequently emerge in the gut and/or the lungs. As a consequence of dysbiosis, there is a disturbance of the level and activation of leucocytes, potentially leading to lung damage. Reintroduction of beneficial microbial strains (i.e., probiotics) may help to recover a healthy status (e.g., microbiota function and composition, leucocyte homeostasis, and/or activation to control infection and immunopathology) through microbiota-derived (e.g., short chain fatty acids) or host-derived products (e.g., cytokines and chemokines) at the local (lung) or distal (gut) level. The "gut-lung axis" refers to the crosstalk between these two mucosal sites of the body

One of the best-known cases is that of segmented filamentous bacteria (SFB), a bacterial lineage of the gut microbiota, which is sufficient to induce the appearance of T-helper (Th)17 cells in the lamina propria in mice. SFB-induced Th17 immunity protects the

host from infection by either intestinal or pulmonary pathogens (Gauguet et al., 2015; Ivanov et al., 2009). Because colonisation of the gut by defined microbial species seems to be important in the context of infectious diseases, it would be interesting to

colonise the lungs with one or several well-defined microbiota species in order to better characterise their local and/or distal role in host immunity development and homeostasis.

3.2 | Chronic bacterial infections: The case of *Mycobacterium tuberculosis*

Chronic infections by the airborne bacterial pathogen *M. tuberculosis*, which causes tuberculosis (TB), can remain latent for years or decades before becoming reactivated and leading to chronic immunopathological lung tissue destruction. Several studies have compared the lung microbiota composition in sputum or bronchoalveolar lavages' fluids, which are more representative of the lower respiratory tract, in TB patients and healthy controls. Although these studies have revealed differences in the airway microbiota composition between patients and controls, the results are not always consistent, likely because of poorly standardised experimental protocols, from initial sampling to sequencing and to the absence of harmonised experimental controls. Six such studies have already been reviewed and summarised by Hong et al (Hong et al., 2016). The same group recently published a meta-analysis study, using the same methods, to reanalyse four of these studies and an additional cohort of healthy individuals (Hong et al., 2018). The authors did not find any difference in the overall global lung microbiota diversity between TB patients and healthy controls. However, they did find that TB patients differed from healthy controls in the abundance of a limited number of bacterial species, with some species being specifically associated with the presence of *M. tuberculosis*.

Gut microbiota has been analysed during the course of TB infections and also during anti-TB treatment in humans. These studies revealed that bacterial diversity in the gut of TB patients is altered and this may correlate with the progress of the disease (Luo et al., 2017; Maji et al., 2018). Anti-TB therapy includes antibiotics, such as rifampicin, that target bacteria other than mycobacteria, and one study showed that prolonged anti-TB treatment broadly alters the gut microbiota of TB patients and that the resulting dysbiotic state persists following cessation of therapy (Wipperman et al., 2017). This suggests that the long anti-TB treatment, which lasts at least 6 months, may render the patients more susceptible to other disorders and infections.

How the gut microbiota influences anti-TB immunity in the lungs is not yet fully understood. Two recent studies have shown that the short chain fatty acid (SCFA) butyrate modulates the production of *M. tuberculosis*-induced pro- and anti-inflammatory cytokines in the lungs, associated with an increased susceptibility to *M. tuberculosis* (Lachmandas et al., 2016; Segal et al., 2017). Because SCFAs, which are produced and released by microbial species of the gut, are mediators of immunity and play a crucial role in gut homeostasis, it remains to be determined whether and how these metabolites could affect the *M. tuberculosis* growth and resilience in the infected host.

The first study addressing the possible functional role of the host microbiota in TB immunity in vivo found that multiplication and dissemination of *M. tuberculosis* were elevated in mice treated with a cocktail of broad-spectrum antibiotics during the course of infection,

and this treatment was associated with a higher number of TB-associated lung lesions (Khan et al., 2016). This correlated with decreased production of tumour necrosis factor (TNF) α -positive and interferon- γ -positive CD4 T cells and an increase of FoxP3-positive regulatory T cells (Treg) in the spleen, suggesting that microbiota dysbiosis following antibiotic treatment adversely altered the immune response to *M. tuberculosis* infection. However, this study did not evaluate the status of local immunity in the lungs of antibiotic-treated animals. More analyses are required to determine the involvement of the host microbiota in the immune response to TB.

4 | TARGETING THE LUNG MICROBIOTA DURING RESPIRATORY DISEASES

In light of our increasing appreciation of the protective role that bacterial commensals play in lung homeostasis, a number of approaches have been developed that target the microbiota-host immune system interaction, with the goal of improving both prevention and treatment of respiratory diseases. Administration of microbes (using probiotics or faecal transfer), microbe components, or products favouring their growth (e.g., prebiotics) has been suggested to confer host protection through direct competition with the disease-causing microbes, enhancement of epithelial barrier functions, or immune modulation during respiratory diseases (Alexandre et al., 2014; Trompette et al., 2018). In this section, we highlight reports of the improved immune responses to lung infections seen upon treatment with probiotics.

Until now, most studies in mice have focused on two infection models—influenza and pneumonia—in which a beneficial effect of oral or nasal probiotic administration has been characterised by improved survival, decreased weight loss, decreased viral titre or bacterial load in the lung, and decreased bronchial epithelium damage (summarised in Table 1). These studies report that the protective effect was mediated by specific immune modulation, distinguished by an early recruitment in the lung of innate leucocytes displaying potent killing properties, such as alveolar macrophages (Park et al., 2013; Vieira et al., 2016), neutrophils (Racedo et al., 2006), or natural killer lymphocytes (Belkacem et al., 2017; Kawahara et al., 2015), and elevated levels of pro-inflammatory cytokines (e.g., TNF- α , IL-6). This inflammatory boost then rapidly diminished, likely due the subsequent increase of anti-inflammatory factors, such as Treg cells and IL-10 in the lungs, reducing lung injuries observed in nontreated mice (Khailova et al., 2013). However, in most studies, causality between immune modulation and host protection has not been demonstrated, and global analysis of the data is complicated by differences in the protocols used for probiotic administration (e.g., oute, dose, and duration).

A number of more experimentally sophisticated studies have recently been published that corroborate the potential of probiotics. Oral administration of *Bifidobacterium longum* has been shown to improve the immune response of *K. pneumoniae*-infected mice, enhancing their survival. It was also shown that the administration in GF mice was able to induce the same beneficial effects as that provided by faecal transfer of whole microbiota (Fagundes et al., 2012; Vieira et al., 2016). This effect may be enacted by acetate production

by *B. longum*, which is consistent with a recent report demonstrating significant protection against *K. pneumoniae* in acetate-treated mice (Galvao et al., 2018).

Concerning administration protocols, comparative studies have suggested that intranasal administration and the use of viable bacteria are the most effective methods for reducing disease features in mice (Youn et al., 2012). It seems that short pretreatment induces a more protective immune response than the classical longer treatments (Racedo et al., 2006). Also, it seems that protection granted against a given pathogen is not only different when using different microbiota species but also between different strains from the same species (Youn et al., 2012). Such results may suggest why, until now, clinical studies using probiotics have shown a promising yet limited potential for the reduction of respiratory disease incidence (Alexandre et al., 2014; Lehtoranta et al., 2014). Therefore, further experimentations helping to identify the most effective strains as well as optimal administration protocols are needed to improve clinical trials.

Lastly, although most commensal bacteria being used as probiotics are of gastrointestinal origin, an alternative strategy is to use natural resident commensal bacteria from the respiratory system. A pioneering study reported the isolation of 20 lower respiratory commensal bacteria species in mice, including *Enterococcus faecalis* that modulates asthma susceptibility in mice (Remot et al., 2017). In the context of infectious diseases, it has been demonstrated that intranasal administration in infant mice of *Corynebacterium pseudodiphtheriticum*, which is present in the respiratory tract, was able to reduce features of both respiratory syncytial virus primary infection and of secondary *S. pneumoniae* superinfection, decreasing both pathogen burden and lung damage (Kanmani et al., 2017).

There has been tremendous progress in leveraging the potential of probiotics in the prevention and treatment of respiratory infections. In spite of this, there is still much more that needs to be done. One key area is extending the successes seen in the various mouse models to the so far more limited successes seen in clinical trials, as already reported for the use of probiotics in intestinal diseases (Suez et al., 2018). Likewise, more detailed studies are needed to address how probiotics (a) modulate the resident lung microbiota community, (b) persist and are localised in airways, (c) interact with resident cells and leucocytes, and (d) influence the homeostasis of lung immunity during and after infection with different pathogens. Finally, we envision the emergence of the characterisation of novel lung microbiota strain interaction with both the local and distal immune systems that could become the next generation of probiotics for respiratory diseases.

5 | PERSPECTIVE

We are only just beginning to understand the functional implications of the lung microbiota in health and disease. It is clear that a much greater research effort needs to be dedicated to uncovering how the lung microbiota interacts and collaborates (or antagonises) with the now increasingly well-studied gut microbiota. Although the existence of a gut–lung axis has been clearly established (Figure 1), the contribution of the airway resident microbiota to this axis remains to be

elucidated. Even if it presently appears difficult to specifically target the lung microbiota without distal effect on other communities, its role needs to be carefully evaluated, possibly by using intranasally delivered antibiotics in order to modify the lung communities (Barfod et al., 2015). Another possible approach involves the introduction, via the oropharyngeal route, of probiotics, which seem to modulate lung immunity, increase protection against respiratory pathogens, and reduce lung damage. Application of these findings in the clinic is moving ever closer, but safety issues concerning the oropharyngeal delivery of living gut or newly identified lung strains remain to be clearly delineated, along with the search for specific active compounds. Similarly, faecal microbial transplantation in humans showed systemic effects (Li et al., 2014) that may prove beneficial in the context of respiratory diseases.

Another outstanding question is whether specific interactions exist between different airways commensals (i.e., trophical niches), as is the case with gut commensals. In addition, even if the great majority of the host microbiota is composed of bacteria, recent evidence has demonstrated that fungal or viral agents can also have beneficial functions (Jiang et al., 2017; Kernbauer et al., 2014) and are a natural part of the lung microbiota (Nguyen et al., 2015; Wylie, 2017), indicating that there is a clear need to better study this (somewhat neglected) aspect of the microbiota during health and disease. In this regard, the use of antifungal and/or antiviral treatments, along with the traditional antibiotic treatments used in mouse models of infections, would represent a highly valuable approach. A potential complication in many studies is the use of laboratory mice confined to highly sterile environments, which is not a representative of the complexity of microbiota present in wild mice and results in altered immune development (Rosshart et al., 2017). Even further complicating this situation, it is known that mice and humans share only 15% microbiota species in the gut (Ley et al., 2005). This is likely similar or even more divergent at other body sites. This will have to be taken into account in future studies.

We envision the application of “omics” studies, such as metagenomics, metabolomics, metatranscriptomics, and metaproteomics, to reduce the gap in knowledge of how the lung microbiome communities affect health and disease. We also encourage functional and mechanistic experimental studies that aim to better understand lung microbial community functions and causality, microbe–microbe and microbe–host cell interactions, as well as inflammatory and resolution pathways/circuits.

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