Received: 3 August 2018 | Revised: 5 October 2018 | Accepted: 14 October 2018

DOI: 10.1111/cmi.12966

MICROREVIEW

WILEY

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

Alexia Dumas | Lucie Bernard | Yannick Poquet | Geanncarlo Lugo-Villarino | Olivier Neyrolles

Institut de Pharmacologie et de Biologie Structurale (IPBS), Université de Toulouse, CNRS, UPS, Toulouse, France

Correspondence

Olivier Neyrolles, Institut de Pharmacologie et de Biologie Structurale (IPBS), Université de Toulouse, CNRS, UPS, Toulouse, France.

Email: olivier.neyrolles@ipbs.fr

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 homoeostasis 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).

https://doi.org/10.1111/cmi.12966

https://doi.org/10.1111/cmi.12968

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; Kostric 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	*Klebsiella pneumoniae*	Survival ↘; CFUs ↗ in blood and lungs; neutrophils, CXCL1, TNFα ↘, and IL-10 ↗ in lungs	IL-10 blocking antibody (s.c.); LPS (i.p.); faecal tranplant (i.g.)	Fagundes et al., 2012
	Streptococcus pneumoniae	CFUs ↗ in lungs	High NOD2-stimulating bacteria group (i.g.)	Brown et al., 2017
	Pseudomonas aeruginosa	Survival ↘; TNFα and IL-1β ↘ in BALF; intestinal epithelial apoptosis ↘		Fox et al., 2012
	P. aeruginosa	CFUs ↗ in lungs and blood		Robak et al., 2018
Antibiotics treated	*Escherichia coli* (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
	K. pneumoniae	CFUs ↗ in lungs; TNFα and IL-6 ↘ in lungs; ROS-mediated killing by AM ↘	NLR ligands (i.g.); AM (i.n.)	Clarke, 2014
	K. pneumoniae *S. pneumoniae*	Survival ↘; CFUs ↗ in lungs; GM-CSF, IL-17A, CXCL1, and CXCL2 ↘ in lungs	Faecal tranplant (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
	S. pneumoniae	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 tranplant (i.g.)	Schuijt et al., 2016
	P. aeruginosa	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
	Mycobacterium tuberculosis	Lungs damages and CFUs ↗ in lungs, spleen, and liver; Treg ↗ and Th1 ↘ in spleen	Faecal tranplant (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)	*Lactobacillus paracasei* 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	*Lactobacillus plantarum* DK119 (i.g. or i.n.)	Park et al., 2013
	Influenza virus	Survival ↗ (highest protection with *Lactobacillus fermentum*-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
	P. aeruginosa	Survival ↗; CFUs and histopathology scores ↘; IL-6 ↘ and IL-10 ↗ in serum and lungs; neutrophils ↘ and Treg ↗ in lungs	*Lactobacillus rhamnosus* GG (i.g.)	Khailova et al., 2013
	S. pneumoniae	CFUs and histopathology scores ↘; specific IgG and IgA ↗ in BALF; neutrophils, TNFα ↗ (early response),	*Lactobacillus casei* (i.g.)	Racedo et al., 2006

(Continues)

TABLE 1 (Continued)

Mouse model	Pathogen studied	Main findings	Phenotype rescue (route of administration)	References
		and ↘ (late response) in serum and lungs; IL-10 ↗ in serum and lungs		
	K. pneumoniae	Survival ↗; body weight loss, CFUs and histopathology score ↘; TNFα and IL-6 in BALF ↘; IL-10 ↗ in lungs; ROS and bacterial killing by AM ↗	*Bifidobacterium longum* 5^{1A}, live, or heat-killed bacteria (i.g.)	Vieira et al., 2016
	RSV and *S. pneumoniae*	Body weight loss, viral titre, CFUs, and histopathology score ↘; IFNβ, IFNγ, TNFα, IL-6, IL-10 ↗ in BALF; DC, AM, CD4 T cells ↗ in lungs	*Corynebacterium pseudodiphtericum* 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.: intransal administration; i.p.: intraperitoneal administration; LPS: lipopolysaccharide; MCP: monocyte chemoattractant protein; MIP: macrophage inflammatory protein; MPO: myeloperoxidase; NF-κB: 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 syncitial virus; s.c.: subcutaneous administration; Th: T-helper lymphocyte; TLR: toll like receptor; TNF: tumour necrosis factor; Treg: regulatory T cells.

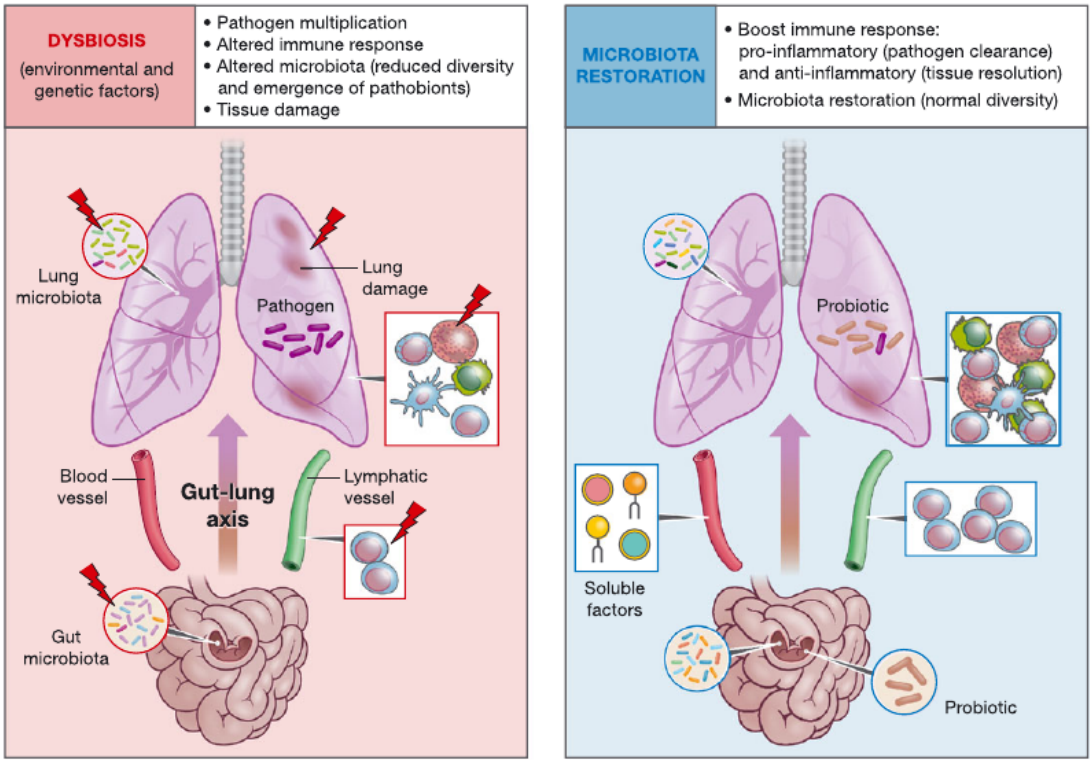

FIGURE 1 Model of the host–microbiota interaction during dysbiosis (and microbiota restoration) within the context of pulmonary infectious disease: the gut–lung axis. The dysbiotic state (i.e., the alteration of the function and composition of the microbiota) can be caused by a variety of environmental (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 homoeostasis, 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 homoeostasis.

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 homoeostasis, 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 homoeostasis, 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 pseudodiphteriticum*, which is present in the respiratory tract, was able to reduce features of both respiratory syncitial 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 homoeostasis 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 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.

FUNDING INFORMATION

The Neyrolles laboratory is supported by the Centre National de la Recherche Scientifique (CNRS), the Université Paul Sabatier-Université de Toulouse, the Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation, the European Union (H2020), the Agence Nationale de la Recherche (ANR), the Fondation Bettencourt-Schueller, and the Fondation pour la Recherche Médicale (FRM). A.D. and L.B. are fellows of the FRM.

ORCID

Olivier Neyrolles http://orcid.org/0000-0003-0047-5885

REFERENCES

Al-Asmakh, M., & Zadjali, F. (2015). Use of germ-free animal models in microbiota-related research. *Journal of Microbiology and Biotechnology*, *25*, 1583–1588. https://doi.org/10.4014/jmb.1501.01039

Alexandre, Y., Le Blay, G., Boisrame-Gastrin, S., Le Gall, F., Hery-Arnaud, G., Gouriou, S., … Le Berre, R. (2014). Probiotics: A new way to fight bacterial pulmonary infections? *Médecine et Maladies Infectieuses*, *44*, 9–17. https://doi.org/10.1016/j.medmal.2013.05.001

Barfod, K. K., Vrankx, K., Mirsepasi-Lauridsen, H. C., Hansen, J. S., Hougaard, K. S., Larsen, S. T., … Krogfelt, K. A. (2015). The murine lung microbiome changes during lung inflammation and intranasal vancomycin treatment. *Open Microbiol J*, *9*, 167–179. https://doi.org/10.2174/1874285801509010167

Belkacem, N., Serafini, N., Wheeler, R., Derrien, M., Boucinha, L., Couesnon, A., … Bourdet-Sicard, R. (2017). *Lactobacillus paracasei* feeding improves immune control of influenza infection in mice. *PLoS One*, *12*, e0184976. https://doi.org/10.1371/journal.pone.0184976

Brestoff, J. R., & Artis, D. (2013). Commensal bacteria at the interface of host metabolism and the immune system. *Nature Immunology*, *14*, 676–684. https://doi.org/10.1038/ni.2640

Brown, R. L., Sequeira, R. P., & Clarke, T. B. (2017). The microbiota protects against respiratory infection via GM-CSF signaling. *Nature Communications*, *8*, 1512. https://doi.org/10.1038/s41467-017-01803-x

Budden, K. F., Gellatly, S. L., Wood, D. L., Cooper, M. A., Morrison, M., Hugenholtz, P., & Hansbro, P. M. (2017). Emerging pathogenic links between microbiota and the gut-lung axis. *Nature Reviews. Microbiology*, *15*, 55–63. https://doi.org/10.1038/nrmicro.2016.142

Charlson, E. S., Bittinger, K., Haas, A. R., Fitzgerald, A. S., Frank, I., Yadav, A., … Collman, R. G. (2011). Topographical continuity of bacterial populations in the healthy human respiratory tract. *American Journal of Respiratory and Critical Care Medicine*, *184*, 957–963. https://doi.org/10.1164/rccm.201104-0655OC

Chen, L. W., Chen, P. H., Hsu, C. M. (2011). Commensal microflora contribute to host defense against Escherichia coli pneumonia through Toll-like receptors. *Shock*, *36*, 67–75. https://doi.org/10.1097/SHK.0b013e3182184ee7

Cheng, M., Chen, Y., Wang, L., Chen, W., Yang, L., Shen, G., … Hu, S. (2017). Commensal microbiota maintains alveolar macrophages with a low level of CCL24 production to generate anti-metastatic tumor activity. *Scientific Reports*, *7*, 7471. https://doi.org/10.1038/s41598-017-08264-8

Clarke, T. B. (2014). Early innate immunity to bacterial infection in the lung is regulated systemically by the commensal microbiota via NOD-like receptor ligands. *Infection and Immunity*, *82*, 4596–4606. https://doi.org/10.1128/IAI.02212-14

Dickson, R. P., & Cox, M. J. (2017). Gut microbiota and protection from pneumococcal pneumonia. *Gut*, *66*, 384.

Dickson, R. P., Erb-Downward, J. R., Falkowski, N. R., Hunter, E. M., Ashley, S. L., & Huffnagle, G. B. (2018). The lung microbiota of healthy mice are highly variable, cluster by environment, and reflect variation in baseline lung innate immunity. *American Journal of Respiratory and Critical Care Medicine*, *198*, 497–508. https://doi.org/10.1164/rccm.201711-2180OC

Dickson, R. P., Erb-Downward, J. R., Freeman, C. M., McCloskey, L., Falkowski, N. R., Huffnagle, G. B., & Curtis, J. L. (2017). Bacterial topography of the healthy human lower respiratory tract. *MBio*, *8*. https://doi.org/10.1128/mBio.02287-16

Dickson, R. P., Martinez, F. J., & Huffnagle, G. B. (2014). The role of the microbiome in exacerbations of chronic lung diseases. *Lancet*, *384*, 691–702. https://doi.org/10.1016/S0140-6736(14)61136-3

Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., … Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *Science*, *308*, 1635–1638. https://doi.org/10.1126/science.1110591

Fagundes, C. T., Amaral, F. A., Vieira, A. T., Soares, A. C., Pinho, V., Nicoli, J. R., … Souza, D. G. (2012). Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. *Journal of Immunology*, *188*, 1411–1420. https://doi.org/10.4049/jimmunol.1101682

Fox, A. C., McConnell, K. W., Yoseph, B. P., Breed, E., Liang, Z., Clark, A. T., … Coopersmith, C. M. (2012). The endogenous bacteria alter gut epithelial apoptosis and decrease mortality following *Pseudomonas aeruginosa* pneumonia. *Shock*, *38*, 508–514. https://doi.org/10.1097/SHK.0b013e31826e47e8

Galvao, I., Tavares, L. P., Correa, R. O., Fachi, J. L., Rocha, V. M., Rungue, M., … Vieira, A. T. (2018). The metabolic sensor GPR43 receptor plays a role in the control of *Klebsiella pneumoniae* infection in the lung. *Frontiers in Immunology*, *9*, 142. https://doi.org/10.3389/fimmu.2018.00142

Gauguet, S., D'Ortona, S., Ahnger-Pier, K., Duan, B., Surana, N. K., Lu, R., … Pier, G. B. (2015). Intestinal microbiota of mice influences resistance to *Staphylococcus aureus* pneumonia. *Infection and Immunity*, *83*, 4003–4014. https://doi.org/10.1128/IAI.00037-15

Hilty, M., Burke, C., Pedro, H., Cardenas, P., Bush, A., Bossley, C., … Cookson, W. O. C. (2010). Disordered microbial communities in asthmatic airways. *PLoS One*, *5*, e8578. https://doi.org/10.1371/journal.pone.0008578

Hong, B. Y., Maulen, N. P., Adami, A. J., Granados, H., Balcells, M. E., & Cervantes, J. (2016). Microbiome changes during tuberculosis and antituberculous therapy. *Clinical Microbiology Reviews*, *29*, 915–926. https://doi.org/10.1128/CMR.00096-15

Hong, B. Y., Paulson, J. N., Stine, O. C., Weinstock, G. M., & Cervantes, J. L. (2018). Meta-analysis of the lung microbiota in pulmonary tuberculosis. *Tuberculosis (Edinburgh, Scotland)*, *109*, 102–108. https://doi.org/10.1016/j.tube.2018.02.006

Ivanov, I. I., Atarashi, K., Manel, N., Brodie, E. L., Shima, T., Karaoz, U., … Littman, D. R. (2009). Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell*, *139*, 485–498. https://doi.org/10.1016/j.cell.2009.09.033

Jiang, T. T., Shao, T. Y., Ang, W. X. G., Kinder, J. M., Turner, L. H., Pham, G., … Way, S. S. (2017). Commensal fungi recapitulate the protective benefits of intestinal bacteria. *Cell Host & Microbe*, *22*, 809–816. e804

Kanmani, P., Clua, P., Vizoso-Pinto, M. G., Rodriguez, C., Alvarez, S., Melnikov, V., … Villena, J. (2017). Respiratory commensal bacteria *Corynebacterium pseudodiphtheriticum* improves resistance of infant mice to respiratory syncytial virus and *Streptococcus pneumoniae* superinfection. *Frontiers in Microbiology*, *8*, 1613. https://doi.org/10.3389/fmicb.2017.01613

Kawahara, T., Takahashi, T., Oishi, K., Tanaka, H., Masuda, M., Takahashi, S., … Suzuki, T. (2015). Consecutive oral administration of *Bifidobacterium longum* MM-2 improves the defense system against influenza virus infection by enhancing natural killer cell activity in a murine model. *Microbiology and Immunology*, *59*, 1–12. https://doi.org/10.1111/1348-0421.12210

Kernbauer, E., Ding, Y., & Cadwell, K. (2014). An enteric virus can replace the beneficial function of commensal bacteria. *Nature*, *516*, 94–98. https://doi.org/10.1038/nature13960

Khailova, L., Baird, C. H., Rush, A. A., McNamee, E. N., & Wischmeyer, P. E. (2013). *Lactobacillus rhamnosus* GG improves outcome in experimental *Pseudomonas aeruginosa* pneumonia: Potential role of regulatory T cells. *Shock*, *40*, 496–503. https://doi.org/10.1097/SHK.0000000000000066

Khan, N., Vidyarthi, A., Nadeem, S., Negi, S., Nair, G., & Agrewala, J. N. (2016). Alteration in the gut microbiota provokes susceptibility to tuberculosis. *Frontiers in Immunology*, *7*, 529.

Khosravi, A., Yanez, A., Price, J. G., Chow, A., Merad, M., Goodridge, H. S., & Mazmanian, S. K. (2014). Gut microbiota promote hematopoiesis to control bacterial infection. *Cell Host & Microbe*, *15*, 374–381. https://doi.org/10.1016/j.chom.2014.02.006

Kostric, M., Milger, K., Krauss-Etschmann, S., Engel, M., Vestergaard, G., Schloter, M., & Scholer, A. (2018). Development of a stable lung

microbiome in healthy neonatal mice. *Microbial Ecology*, *75*, 529–542. https://doi.org/10.1007/s00248-017-1068-x

Lachmandas, E., van den Heuvel, C. N., Damen, M. S., Cleophas, M. C., Netea, M. G., & van Crevel, R. (2016). Diabetes mellitus and increased tuberculosis susceptibility: The role of short-chain fatty acids. *J Diabetes Res*, *2016*, 6014631. https://doi.org/10.1155/2016/6014631

Lankelma, J. M., Schuijt, T. J., & Wiersinga, W. J. (2017). Reply to letter to the editor of gut by Dickson and Cox. *Gut*, *66*, 556.

Lehtoranta, L., Pitkaranta, A., & Korpela, R. (2014). Probiotics in respiratory virus infections. *European Journal of Clinical Microbiology & Infectious Diseases*, *33*, 1289–1302. https://doi.org/10.1007/s10096-014-2086-y

Levy, M., Kolodziejczyk, A. A., Thaiss, C. A., & Elinav, E. (2017). Dysbiosis and the immune system. *Nature Reviews. Immunology*, *17*, 219–232. https://doi.org/10.1038/nri.2017.7

Ley, R. E., Backhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut microbial ecology. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 11070–11075. https://doi.org/10.1073/pnas.0504978102

Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Microbial ecology: Human gut microbes associated with obesity. *Nature*, *444*, 1022–1023. https://doi.org/10.1038/4441022a

Li, Q., Wang, C., Tang, C., He, Q., Zhao, X., Li, N., & Li, J. (2014). Therapeutic modulation and reestablishment of the intestinal microbiota with fecal microbiota transplantation resolves sepsis and diarrhea in a patient. *The American Journal of Gastroenterology*, *109*, 1832–1834. https://doi.org/10.1038/ajg.2014.299

Limon, J. J., Skalski, J. H., & Underhill, D. M. (2017). Commensal fungi in health and disease. *Cell Host & Microbe*, *22*, 156–165. https://doi.org/10.1016/j.chom.2017.07.002

Lopez-Siles, M., Khan, T. M., Duncan, S. H., Harmsen, H. J., Garcia-Gil, L. J., & Flint, H. J. (2012). Cultured representatives of two major phylogroups of human colonic *Faecalibacterium prausnitzii* can utilize pectin, uronic acids, and host-derived substrates for growth. *Applied and Environmental Microbiology*, *78*, 420–428. https://doi.org/10.1128/AEM.06858-11

Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, *489*, 220–230. https://doi.org/10.1038/nature11550

Luo, M., Liu, Y., Wu, P., Luo, D. X., Sun, Q., Zheng, H., … Zeng, Y. (2017). Alternation of gut microbiota in patients with pulmonary tuberculosis. *Frontiers in Physiology*, *8*, 822. https://doi.org/10.3389/fphys.2017.00822

Mahowald, M. A., Rey, F. E., Seedorf, H., Turnbaugh, P. J., Fulton, R. S., Wollam, A., … Gordon, J. I. (2009). Characterizing a model human gut microbiota composed of members of its two dominant bacterial phyla. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 5859–5864. https://doi.org/10.1073/pnas.0901529106

Maji, A., Misra, R., Dhakan, D. B., Gupta, V., Mahato, N. K., Saxena, R., … Singh, Y. (2018). Gut microbiome contributes to impairment of immunity in pulmonary tuberculosis patients by alteration of butyrate and propionate producers. *Environmental Microbiology*, *20*, 402–419. https://doi.org/10.1111/1462-2920.14015

Man, W. H., de Steenhuijsen Piters, W. A., & Bogaert, D. (2017). The microbiota of the respiratory tract: Gatekeeper to respiratory health. *Nature Reviews. Microbiology*, *15*, 259–270. https://doi.org/10.1038/nrmicro.2017.14

Marsland, B. J., & Gollwitzer, E. S. (2014). Host-microorganism interactions in lung diseases. *Nature Reviews. Immunology*, *14*, 827–835. https://doi.org/10.1038/nri3769

Mirzaei, M. K., & Maurice, C. F. (2017). Menage a trois in the human gut: Interactions between host, bacteria and phages. *Nature Reviews. Microbiology*, *15*, 397–408. https://doi.org/10.1038/nrmicro.2017.30

Morris, A., Beck, J. M., Schloss, P. D., Campbell, T. B., Crothers, K., Curtis, J. L., … Lung HIV Microbiome Project (2013). Comparison of the respiratory microbiome in healthy nonsmokers and smokers. *American Journal of Respiratory and Critical Care Medicine*, *187*, 1067–1075. https://doi.org/10.1164/rccm.201210-1913OC

Nelson, A. M., Walk, S. T., Taube, S., Taniuchi, M., Houpt, E. R., Wobus, C. E., & Young, V. B. (2012). Disruption of the human gut microbiota following norovirus infection. *PLoS One*, *7*, e48224. https://doi.org/10.1371/journal.pone.0048224

Nguyen, L. D., Viscogliosi, E., & Delhaes, L. (2015). The lung mycobiome: An emerging field of the human respiratory microbiome. *Frontiers in Microbiology*, *6*, 89.

Park, M. K., Ngo, V., Kwon, Y. M., Lee, Y. T., Yoo, S., Cho, Y. H., … Kang, S. M. (2013). *Lactobacillus plantarum* DK119 as a probiotic confers protection against influenza virus by modulating innate immunity. *PLoS One*, *8*, e75368. https://doi.org/10.1371/journal.pone.0075368

Peterson, J., Garges, S., Giovanni, M., McInnes, P., Wang, L., Schloss, J. A., … Guyer, M. (2009). The NIH Human Microbiome Project. *Genome Research*, *19*, 2317–2323. https://doi.org/10.1101/gr.096651.109

Pragman, A. A., Kim, H. B., Reilly, C. S., Wendt, C., & Isaacson, R. E. (2012). The lung microbiome in moderate and severe chronic obstructive pulmonary disease. *PLoS One*, *7*, e47305. https://doi.org/10.1371/journal.pone.0047305

Racedo, S., Villena, J., Medina, M., Aguero, G., Rodriguez, V., & Alvarez, S. (2006). *Lactobacillus casei* administration reduces lung injuries in a *Streptococcus pneumoniae* infection in mice. *Microbes and Infection*, *8*, 2359–2366. https://doi.org/10.1016/j.micinf.2006.04.022

Remot, A., Descamps, D., Noordine, M. L., Boukadiri, A., Mathieu, E., Robert, V., … Thomas, M. (2017). Bacteria isolated from lung modulate asthma susceptibility in mice. *The ISME Journal*, *11*, 1061–1074. https://doi.org/10.1038/ismej.2016.181

Robak, O. H., Heimesaat, M. M., Kruglov, A. A., Prepens, S., Ninnemann, J., Gutbier, B., … Opitz B. (2018). Antibiotic treatment-induced secondary IgA deficiency enhances susceptibility to Pseudomonas aeruginosa pneumonia. *The Journal of Clinical Investigation*, *128*, 3535–3545. https://doi.org/10.1172/JCI97065

Rosshart, S. P., Vassallo, B. G., Angeletti, D., Hutchinson, D. S., Morgan, A. P., Takeda, K., … Rehermann, B. (2017). Wild mouse gut microbiota promotes host fitness and improves disease resistance. *Cell*, *171*, 1015–1028. e1013

Samuelson, D. R., Shellito, J. E., Maffei, V. J., Tague, E. D., Campagna, S. R., Blanchard, E. E., … Welsh, D. A. (2017). Alcohol-associated intestinal dysbiosis impairs pulmonary host defense against *Klebsiella pneumoniae*. *PLoS Pathogens*, *13*, e1006426. https://doi.org/10.1371/journal.ppat.1006426

Schuijt, T. J., Lankelma, J. M., Scicluna, B. P., de Sousa e Melo, F., Roelofs, J. J. T. H., de Boer, J. D., … Wiersinga, W. J. (2016). The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia. *Gut*, *65*, 575–583. https://doi.org/10.1136/gutjnl-2015-309728

Segal, L. N., Clemente, J. C., Li, Y., Ruan, C., Cao, J., Danckers, M., … Weiden, M. D. (2017). Anaerobic bacterial fermentation products increase tuberculosis risk in antiretroviral-drug-treated HIV patients. *Cell Host & Microbe*, *21*, 530–537 e534.

Sender, R., Fuchs, S., & Milo, R. (2016). Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology*, *14*, e1002533. https://doi.org/10.1371/journal.pbio.1002533

Suez, J., Zmora, N., Zilberman-Schapira, G., Mor, U., Dori-Bachash, M., Bashiardes, S., … Elinav, E. (2018). Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell*, *174*, 1406–1423 e1416.

Taylor, S. L., Wesselingh, S., & Rogers, G. B. (2016). Host-microbiome interactions in acute and chronic respiratory infections. *Cellular Microbiology*, *18*, 652–662. https://doi.org/10.1111/cmi.12589

Trompette, A., Gollwitzer, E. S., Pattaroni, C., Lopez-Mejia, I. C., Riva, E., Pernot, J., … Marsland, B. J. (2018). Dietary fiber confers protection against flu by shaping Ly6c(−) patrolling monocyte hematopoiesis and CD8(+) T cell metabolism. *Immunity*, *48*, 992–1005. e1008

Trompette, A., Gollwitzer, E. S., Yadava, K., Sichelstiel, A. K., Sprenger, N., Ngom-Bru, C., … Marsland, B. J. (2014). Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nature Medicine*, *20*, 159–166. https://doi.org/10.1038/nm.3444

Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, *444*, 1027–1031. https://doi.org/10.1038/nature05414

Vieira, A. T., Rocha, V. M., Tavares, L., Garcia, C. C., Teixeira, M. M., Oliveira, S. C., … Nicoli, J. R. (2016). Control of *Klebsiella pneumoniae* pulmonary infection and immunomodulation by oral treatment with the commensal probiotic *Bifidobacterium longum* 5(1A). *Microbes and Infection*, *18*, 180–189. https://doi.org/10.1016/j.micinf.2015.10.008

Willner, D., Haynes, M. R., Furlan, M., Schmieder, R., Lim, Y. W., Rainey, P. B., … Conrad, D. (2012). Spatial distribution of microbial communities in the cystic fibrosis lung. *The ISME Journal*, *6*, 471–474. https://doi.org/10.1038/ismej.2011.104

Wipperman, M. F., Fitzgerald, D. W., Juste, M. A. J., Taur, Y., Namasivayam, S., Sher, A., … Glickman, M. S. (2017). Antibiotic treatment for tuberculosis induces a profound dysbiosis of the microbiome that persists long after therapy is completed. *Scientific Reports*, *7*, 10767. https://doi.org/10.1038/s41598-017-10346-6

Wylie, K. M. (2017). The virome of the human respiratory tract. *Clinics in Chest Medicine*, *38*, 11–19. https://doi.org/10.1016/j.ccm.2016.11.001

Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., … Gordon, J. I. (2012). Human gut microbiome viewed across age and geography. *Nature*, *486*, 222–227. https://doi.org/10.1038/nature11053

Youn, H. N., Lee, D. H., Lee, Y. N., Park, J. K., Yuk, S. S., Yang, S. Y., … Song, C. S. (2012). Intranasal administration of live lactobacillus species facilitates protection against influenza virus infection in mice. *Antiviral Research*, *93*, 138–143. https://doi.org/10.1016/j.antiviral.2011.11.004

Zhang, M., Jiang, Z., Li, D., Jiang, D., Wu, Y., Ren, H., … Lai, Y. (2015). Oral antibiotic treatment induces skin microbiota dysbiosis and influences wound healing. *Microbial Ecology*, *69*, 415–421. https://doi.org/10.1007/s00248-014-0504-4

How to cite this article: Dumas A, Bernard L, Poquet Y, Lugo-Villarino G, Neyrolles O. The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases. *Cellular Microbiology*. 2018;20:e12966. https://doi.org/10.1111/cmi.12966