Cellular Microbiology (2016) **18**(5), 652–662 doi:10.1111/cmi.12589

Microreview

Host-microbiome interactions in acute and chronic respiratory infections

Steven L. Taylor, Steve Wesselingh and Geraint B. Rogers*

SAHMRI Infection and Immunity Theme, School of Medicine, Flinders University, Bedford Park, Adelaide, Australia.

Summary

Respiratory infection is a leading cause of global morbidity and mortality. Understanding the factors that influence risk and outcome of these infections is essential to improving care. We increasingly understand that interactions between the microbial residents of our mucosal surfaces and host regulatory systems is fundamental to shaping local and systemic immunity. These mechanisms are most well defined in the gastrointestinal tract, however analogous systems also occur in the airways. Moreover, we now appreciate that the host–microbiota interactions at a given mucosal surface influence systemic host processes, in turn, affecting the course of infection at other anatomical sites. This review discusses the mechanisms by which the respiratory microbiome influences acute and chronic airway disease and examines the contribution of cross-talk between the gastrointestinal and respiratory compartments to microbe–mucosa interactions.

The potential of commensal microbes to contribute to human physiology has long been recognized (Tappeiner, 1884). However, our understanding of the clinical importance of these interkingdom interactions has increased dramatically in recent years with the development and application of omics technologies (Rogers, 2015). We now recognize that the colonization of many of our mucosal surfaces, particularly those in the colon, is necessary for the normal development of immune function (Kaplan *et al.*, 2011; Karmarkar and Rock, 2013), metabolic regulation (Goulet, 2015) and even brain function, behaviour and cognition (Cryan and O'Mahony, 2011; Foster and McVey Neufeld, 2013). The functional effects of microbes are mediated via bidirectional host–microbe interactions, the importance of which is reflected in the increasing number of conditions that are associated with their disruption (Vijay-Kumar *et al.*, 2010; Wood, 2012; Serino *et al.*, 2014; Lurie *et al.*, 2015; Mira-Pascual *et al.*, 2015; Zhang *et al.*, 2015).

Progress in understanding these highly complex microbial systems has benefitted from conceptual as well as technological advances. It is now appreciated that the characteristics of a microbial community can be distinct from the characteristics of the taxa that it comprises (Rogers *et al.*, 2010). The development of analytical strategies that take into account the spatial heterogeneity and temporal variability of many of the body's mucosal systems, factors that are intrinsically linked to host homeostasis (Marcobal *et al.*, 2013; Hubbard *et al.*, 2015), has also been necessary. Together, these advances have led to the enhancement of disease research, enabling more comprehensive investigations of interactions between the microbiome and human physiology at various body sites and clinical contexts.

Most of the microbiome research undertaken to date has focused on bacterial communities in the colon, the site of the largest and most complex microbial system in the body. However, resident polymicrobial communities exist at many other body sites, including the skin (Grice, 2015), and the genitourinary (Brotman *et al.*, 2014) and respiratory tracts (Neish, 2014; Vissers *et al.*, 2014). In each case, bidirectional communication between microbes and the underlying tissue regulates the local environment, including physical characteristics as well as immunity.

In this review, we examine parallels in host–microbe interactions between the gastrointestinal and respiratory tracts, with an emphasis on the respiratory tract during health, acute infection and chronic infection. We then discuss the interconnectedness of organ systems and ways in which communication between the gastrointestinal and respiratory tracts can influence respiratory disease outcomes.

Received 29 January, 2016; accepted 3 March, 2016. *For correspondence. E-mail geraint.rogers@sahmri.com; Tel. 618 8204 7614; Fax 618 8204 4733.

The respiratory microbiome

Gaining a better understanding of the respiratory microbiome will provide an important basis for the treatment, management or prevention of respiratory illnesses. The disruption of respiratory microbial communities has been implicated in dysregulation of local immunity (Hansel *et al*., 2013), infection susceptibility (Vissers *et al*., 2014) and the development of chronic respiratory inflammatory diseases (Marsland and Gollwitzer, 2014), which collectively account for more than 1 in 10 of all deaths worldwide (World Health Organization, 2014).

Arising from the foregut during embryonic development, the airways share many structural and physiological features with the gastrointestinal tract (Morrisey and Hogan, 2010). Both systems feature a large, vascularized luminal epithelium coated by a mucus layer (Keely *et al*., 2012), and both have mucosa-associated lymphoid tissues that facilitate local immune responses (Elmore, 2006). Dynamic microbial colonization occurs in early-life in both compartments (Koenig *et al*., 2011; Biesbroek *et al*., 2014), and ultimately both sites present spatially differentiated microbiota in terms of bacterial composition and overall abundance (Zhang *et al*., 2014; Venkataraman *et al*., 2015) (Fig. 1). While the role played by microbial interactions in the gut during development are now well recognized, less is known about the parallel processes that take place in the airways.

The contribution made by resident microbes to the regulation of airway physiology and response to infection begins soon after birth. In a process comparable to the bacterial colonization of the gut, the assembly of a respiratory microbiota appears to follow an ordered progression that is linked to subsequent immune phenotype. The nasopharynx is initially colonized by bacterial taxa that include the genera *Staphylococcus* or *Corynebacterium*, later replaced by *Moraxella* or *Alloiococcus*,

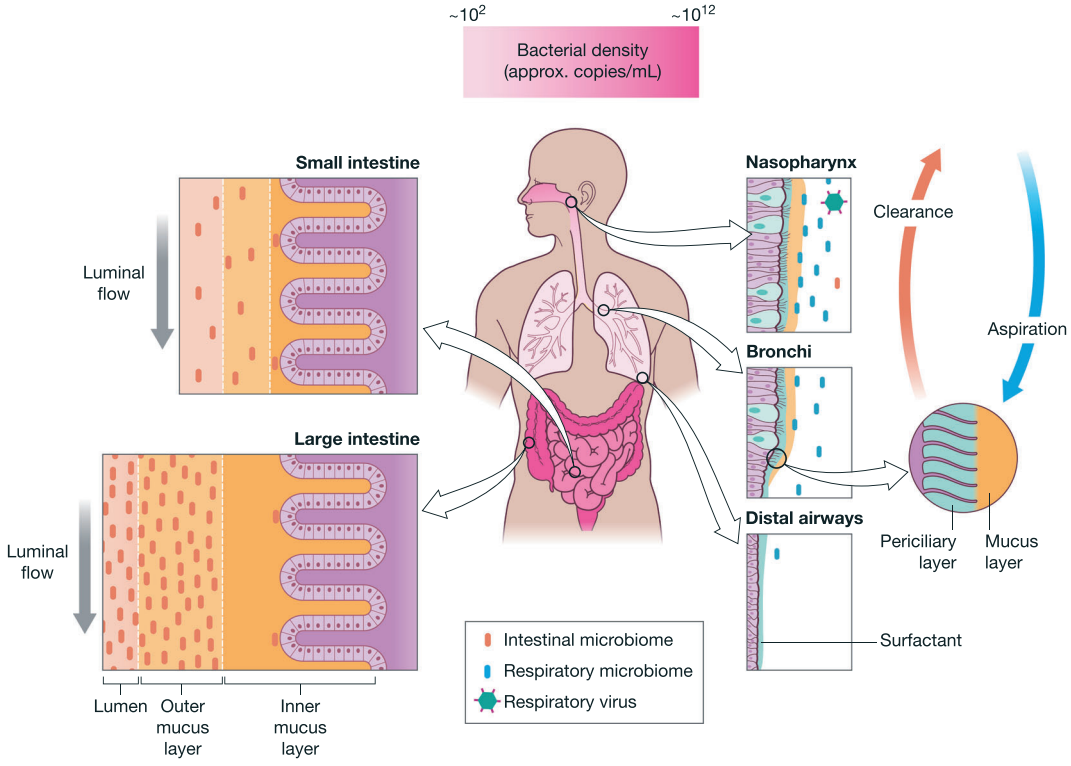

Fig. 1. Mucosal surfaces of the gastrointestinal tract and respiratory tract in health, highlighting regiospecific diversity in epithelia, mucus thickness and microbial colonization at each site. The gastrointestinal tract consists of inner and outer mucus layers, which vary in thickness regionally. The inner mucus layer is dense and largely free of microbes, while the outer layer is heavily colonized by bacteria and is more easily removed during luminal flow. The small intestine contains approximately 10^5–10^7 bacteria per gram while the large intestine contains approximately 10^{10}–10^{12} bacteria per gram. Certain bacteria can penetrate the mucus and reside closer to the epithelium. Composition also varies regionally throughout the intestines (not shown). The respiratory tract consists of a single-layered secreted mucus layer in the upper and conducting airways, which sits atop a periciliary layer made up of less viscous membrane bound mucus attached to the underlying stratified ciliated epithelium. The nasopharyngeal space harbours a resident microbiome of approximately 10^5 bacteria per millilitre of nasopharyngeal wash and is exposed to aspirated microbes. The conducting airways, consisting of the trachea and bronchial branches, harbour a non-replicating community of approximately 10^3–10^4 bacteria per millilitre of lavage fluid, which is constantly turned over by immigration and elimination factors. Toward the distal airways, the epithelium becomes thinner, cuboidal, non-ciliated and the periciliary layer transitions into a layer of surfactant. This area is largely sterile. Controlled ciliary beating as well as coughing reflex move mucus upwards from the conducting distal to proximal airways moving inhaled particles and microbes with it.

and punctuated by transient acquisition of *Streptococcus* or *Haemophilus* species (Bisgaard *et al*., 2011; Bogaert *et al*., 2011; Teo *et al*., 2015). Corresponding rates of maternal and infant *Staphylococcus aureus* colonization (Schaumburg *et al*., 2014) implicate vertical transmission in this process, paralleling that seen in the gut (Koenig *et al*., 2011). Not only does the colonization of the gut and upper respiratory tract (URT) occur at the same time, but there is evidence of substantial cross-talk between the two sites., 2012), including synchronized fluctuations in the abundance of a number of bacterial taxa (Madan *et al*., 2012).

While respiratory microbiome research is relatively new, the distribution of colonizing microbial populations throughout the airways is thought to be shaped by an array of immune mechanisms. Alveolar monocytes and macrophages, as well as dendritic cells, $CD4^+$ T cells and innate lymphoid cells, that reside in the lower respiratory tract (LRT), prevent the establishment of substantial populations in the lower airways (Holt *et al*., 2008) and largely confine microbes to the URT. In addition a denser, more nutrient rich mucus layer is present in the URT, which facilitates microbial growth and replication, while the lower airways are coated in low-nutrient surfactant (Fahy and Dickey, 2010) (Fig. 1).

The impact of other potentially selective properties, such as mucin gene expression, mucin hydration, oxygen tension and pH balance, which all vary throughout the lung (West, 1968; Thornton *et al*., 2008), on microbial composition is poorly understood. Spatial differences may also occur vertically through the respiratory mucus layer. In the gut, for example, some bacterial species can penetrate the mucus and reside close to the epithelium (Johansson *et al*., 2008; Vaishnava *et al*., 2011; Atarashi *et al*., 2015), while the majority are mucus-associated, or located primarily in the lumen (Hill *et al*., 2010). The extent to which this also occurs in the thinner mucus layers of the URT is not well described nor is the contribution of microbial activity to the regulation of airway mucosa gene expression. Clear differences in the structural diversity of glycans exist along the intestinal tract (Robbe *et al*., 2004), some of which are bacteria-dependent (Freitas *et al*., 2002), but again, whether an analogous situation exists in the airways is not known.

The overall effect of this regiospecific heterogeneity is the development of a substantial resident bacterial community in the mucosae of the upper airways, but which declines in abundance in the conducting airways, and peters down to a largely uncolonized non-ciliated squamous epithelium of the lower bronchioles and lung parenchyma (Fig. 1). Although microbes have been consistently detected in the LRT of healthy individuals (Charlson *et al*., 2011; Erb-Downward *et al*., 2011; Dickson *et al*., 2015), this likely represents an ongoing process of microaspiration and clearance that maintains the lungs in a state which is largely free from substantial colonization. This model is supported by the similarity in composition of microbiota in the upper and distal airways, suggesting that the former act as the principal source of microaspirated bacteria, and substantial proliferation under altered selective conditions is absent in the latter (Venkataraman *et al*., 2015).

The respiratory microbiome and infection

The importance of airway colonization for regulation of local immunity is reflected in a large number of studies that have linked airway dysbiosis with infection or disease development. For example, LRT infections in early life have been shown to predispose infants to early allergic sensitization and risk of persistent wheeze in later childhood (Kusel *et al*., 2007; Jackson *et al*., 2008; Holt *et al*., 2010). Infection is not necessary for this relationship, with asymptomatic colonization of taxa such as *Streptococcus pneumoniae*, *Moraxella catarrhalis* and/or *Haemophilus influenzae* also linked to the development of chronic wheeze (Bisgaard *et al*., 2011; Teo *et al*., 2015). Furthermore, the composition of the nasopharyngeal microbiota at six weeks of age has been shown to be correlated with microbiota stability over the first two years of life, as well as with rates of respiratory infection (Biesbroek *et al*., 2014). This association is not unidirectional, and symptomatic URT viral infection has been found to precede URT bacterial outgrowth (Bosch *et al*., 2013; Molyneaux *et al*., 2013).

The mechanisms by which the nascent upper airway microbiota shape local and systemic immunity remain poorly understood. However, changes to lung microbial composition in neonatal mice during development have been shown to be associated with regulatory T-cell-dependent allergen tolerance (Gollwitzer *et al*., 2014). Modulation of the URT microbiome in early life, for example, by the nasal administration of *Lactobacillus rhamnosus* or *Lactococcus lactis*, has also been shown to provide subsequent protection against respiratory syncytial virus (Tomosada *et al*., 2013), and increased clearance of *S. pneumoniae* from lung (Medina *et al*., 2008), respectively, with both innate and specific immune responses in local and systemic compartments implicated. Such observations suggest that disruption of normal upper airway colonization, resulting from factors such as antibiotic exposure or infection, has long-term health implications, though assignment of causality is difficult (Semic-Jusufagic *et al*., 2014).

Acute LRT infections

The respiratory tract is the main portal for acute infection, and, of these, infections in the LRT represent a substantial global healthcare burden (World Health Organization,

2014). Acute LRT infections typically involve the rapid expansion of an opportunistic pathogen population, which if not cleared, can progress systemically. A primary source of LRT infections is the URT (de Steenhuijsen Piters *et al*., 2015), whereby the balance between the entry of microbes into the lower airways and their removal becomes tipped toward colonization (Dickson *et al*., 2015). Increased entry of microbes to the LRT may occur during pathogen overgrowth in the URT as a result of both newly available niche space and the removal of commensal species that would otherwise exert a suppressive influence on potential pathogens (Abreu *et al*., 2012). Subsequent acute LRT infection can be further enhanced by host factors such as impaired LRT clearance mechanisms, or microbial factors such as pathogen synergy.

Impaired clearance mechanisms such as physical obstruction, as seen in intubated patients, or immune senescence, as seen in the elderly, increase risk of LRT infection. In intubated patients, where the presence of an endotracheal tube acutely impairs mucociliary motility and cough reflex, there is an increased risk of LRT infection as a result of pooling of oropharyngeal microbes on the endotracheal tube, which move into the lungs, causing ventilator-associated pneumonia (Mietto *et al*., 2013). Immune senescence, in the elderly, is associated with reduced mucociliary function (de Oliveira-Maul *et al*., 2013) and a dampened immune responses (Haq and McElhaney, 2014). These impaired mechanisms, combined with poor oral health, are associated with bacteria from the URT infiltrating the LRT, causing pneumonia (El-Solh, 2011).

While acute LRT infections are often associated with a single pathogen, synergistic interactions between microbes, either direct or mediated by the host, can also facilitate infection. A notable example is the bacterial pneumonia that can follow influenza infection. Primary infection with influenza virus and subsequent local immune response leads to acute increased mucus production, resulting in higher concentrations of sialylated MUC5AC glycoproteins in the URT. *Streptococcus pneumoniae* encodes a sialic acid catabolism gene locus that allows it to utilize sialic acid as a carbon source, expand more rapidly, and cause secondary LRT infection (Siegel *et al*., 2014). Analogous examples of the ability of pathogens to exploit the host epithelial response to facilitate LRT infection also exist in chronic LRT infections.

Chronic LRT infections

Chronic LRT infections are associated with conditions such as cystic fibrosis (CF), non-CF bronchiectasis, chronic obstructive pulmonary disorder and primary ciliary dyskinesia (Stressmann *et al*., 2012; Rogers *et al*., 2013a,2013b; Galiana *et al*., 2014). In contrast to acute infections, chronic polymicrobial lung conditions arise as a result of underlying immune dysregulation, allowing a stable and complex infective microbiota to become established.

The presence of bacteria in the lower airways is a major driver of inflammation-induced airway damage in chronic respiratory diseases. Stimulation of toll-like receptors (TLRs) from bacterial products trigger the dis-inhibition of NF-κB, a key regulating transcription factor of genes that are involved in immune infiltration (Lawrence, 2009). The sustained influx of neutrophils that follows leads to an accumulation of factors that cause further host damage, including reactive oxygen species, reactive nitrogen intermediates, activated matrix metalloproteinases and neutrophil elastase (Kolaczkowska and Kubes, 2013), with factors implicated in airway remodelling related to the composition of the infective microbiota (Taylor *et al*., 2015). At the same time, the neutrophilic release of pro-inflammatory mediators and chemoattractants perpetuates inflammatory cell infiltration (Elizur *et al*., 2008). The expression of bacterial virulence traits themselves can also contribute substantially to epithelial damage, as can the production of noxious metabolites such as hydrogen cyanide that result from growth (Ryall *et al*., 2009).

Along with airway damage, local inflammation or direct TLR activation also induce the NF-κB pathway in respiratory goblet cells. This interaction triggers the goblet cell transcription programme SPDEF/FOXA3, promoting mucin hypersecretion, and goblet cell hyperplasia and metaplasia, ultimately increasing goblet cell numbers and overall mucus production, which are hallmarks of chronic respiratory disease (Fahy and Dickey, 2010). Molecular changes to the mucin glycoproteins themselves also occur as a result of chronic inflammation, affecting airway colonization. For example, patients with chronic bronchitis and CF were found to exhibit altered sialylation, fucosylation and sulfonation of sputum mucin proteins (Rose and Voynow, 2006). Mucin glycans are a primary source of nutrients, as well as adhesion sites for bacteria and fungi in diseased airways, with different microbes able to utilize specific glycans (Audfray *et al*., 2013). Somewhat analogous to the *S. pneumoniae* acute secondary infection described in the preceding texts, *Pseudomonas aeruginosa* preferentially binds to highly sialylated mucin glycans (Scharfman *et al*., 1999), and hence adheres to CF mucin over non-CF mucin (Devaraj *et al*., 1994). Inhalation of glycans that *P. aeruginosa* bind to has been shown to reduce *P. aeruginosa* load in the lungs of patients with CF, most likely by acting as receptor decoys and limiting biofilm formation and epithelial adhesion (Hauber *et al*., 2008; Boukerb *et al*., 2014).

Disruption of interspecies interactions within chronic LRT infections is emerging as a potential strategy to break the cycle of infection, inflammation and remodelling often associated with chronic LRT infections (Cole, 1986). The

contribution of interspecies interactions in shaping the expression of pathogenicity traits by microbiota members is increasingly appreciated. An example of this can be seen in the complex infections that affect the lungs of patients with CF. These infections are often dominated by *P. aeruginosa*; however, an increase in the abundance of *Streptococcus milleri* has been found to precede pulmonary exacerbations (Sibley *et al*., 2008b). While not at a high abundance, the presence of non-pathogenic oropharyngeal bacteria profoundly influences the pathogenicity of *P. aeruginosa* (Sibley *et al*., 2008a; Quinn *et al*., 2015). The mechanisms that underpin such relationships include metabolic interactions that help opportunistic pathogens to adapt to the challenging conditions of the lung (Venkataraman *et al*., 2014; Mirkovic *et al*., 2015; Quinn *et al*., 2015) and interspecies signalling pathways (Duan *et al*., 2003; Ryan *et al*., 2008).

Gut-lung axis

While the airway microbiota locally regulates immune function, the gastrointestinal microbiome can also influence respiratory immunity, via the gut-lung axis. Indeed, advances in systems physiology demonstrate the interconnectedness of host organs and their microbial influences, with recent findings identifying the role of a gut-liver axis (Boursier *et al*., 2015), a gut-brain axis (Weber, 2015) and a gut-skin axis (Abrahamsson *et al*., 2012), in mediating a range of infection or disease scenarios.

A clear example of the contribution of the gut-lung axis to the regulation of local immunity in the respiratory tract is in asthma, where disruption of the early-life microbial colonization of the gut has a well-supported relationship with airway allergen sensitization (Bjorksten *et al*., 2001; Johnson *et al*., 2005; Bisgaard *et al*., 2011; Russell *et al*., 2015). Disruption of gut microbiome development, during infancy also increases susceptibility to lung infection (Biesbroek *et al*., 2014), suggesting that the gut microbiome plays an important role in early-life lung immune development (Zeissig and Blumberg, 2014).

The interaction of microbiota-related regulatory mechanisms in the gut and the development of lung disease are not limited to early life, as indicated by the ongoing role played by the gut microbiota in maintaining and regulating systemic immunity. For example, the expansion and differentiation of extra-intestinal T-cell populations, which are important for systemic immunity, are mediated by the intestinal microbiota (Sudo *et al*., 2004; Atarashi *et al*., 2013). Similarly, the degree of macrophage response to respiratory viral infections is dependent on the presence of gut microbes, suggesting that intestinal microbial stimulation is integral in calibrating the activation threshold for an innate antiviral immune response (Abt *et al*., 2012). Gut-initiated TLR signalling has been shown to mediate this effect, as illustrated by the restoration of lung $CD4^+$ and $CD8^+$ T cells and improved survival to influenza infection following a single dose of LPS delivered intrarectally into adult antibiotic treated mice (Ichinohe *et al*., 2011).

The influence of gut microbes on respiratory immunity is further illustrated by the effects of ingested probiotics and prebiotics on respiratory infections and diseases. Probiotics have been shown to reduce the incidence of CF pulmonary exacerbations (Bruzzese *et al*., 2007; Weiss *et al*., 2010) and improve allergic rhinitis (Wang *et al*., 2004; Giovannini *et al*., 2007), while prebiotics that alter the gut microbiota composition and function, such as dietary fibre, protect against allergic airway disease through the production of immunomodulatory short chain fatty acids (SCFAs) (Trompette *et al*., 2014). Indeed, SCFAs are likely to contribute to an array of host-modulatory pathways because of their ability to exert broad anti-inflammatory activities, including affecting immune cell migration, adhesion, cytokine expression, as well as cellular proliferation, activation and apoptosis through the activation of signalling pathways (NF-κB) and inhibition of histone deacetylase (Samuelson *et al*., 2015).

Given the importance of these immune-regulatory pathways, disruption of the gut microbiome has clear potential to influence lung disease outcomes. Dysbiosis-mediated inflammation can result in increases in circulating cytokines and chemokines, including increased levels of faecal calprotectin, plasma C-reactive protein, IL-6 and IL-8 (Biagi *et al*., 2010; Verdam *et al*., 2013), which could contribute to the morbidity in other physiological systems, such as the lung. Negative associations have been found between increased levels of faecal calprotectin and lung function in adult patients with CF (Adriaanse *et al*., 2015). Levels of faecal calprotectin also appear to be predictive of response to treatment of CF pulmonary exacerbations (Sagel *et al*., 2015), suggesting that a direct link might exist between CF enteropathy and respiratory decline. Gut dysbiosis might also contribute to outcomes in chronic respiratory disease by reducing nutrient and energy harvest (Guarner and Malagelada, 2003), in turn, undermining a patient's ability to mount an effective immune response. There is also evidence that inflammatory mediators can spill over from the lung (Teichert *et al*., 2014) and impact distal organs, including the gut (Liu *et al*., 2014).

It is important to recognize that the interaction between the gut and respiratory microbiota is not unidirectional. Respiratory viral infections are often accompanied by intestinal symptoms (Dilantika *et al*., 2010; Wang *et al*., 2014), leading to intestinal immune injury and inflammation. Chronic lung infections have been shown to contribute to inflammatory spill-over (Gan *et al*., 2004), with knock-on effects likely for the gut environment. Furthermore, treatments for lung infections, particularly

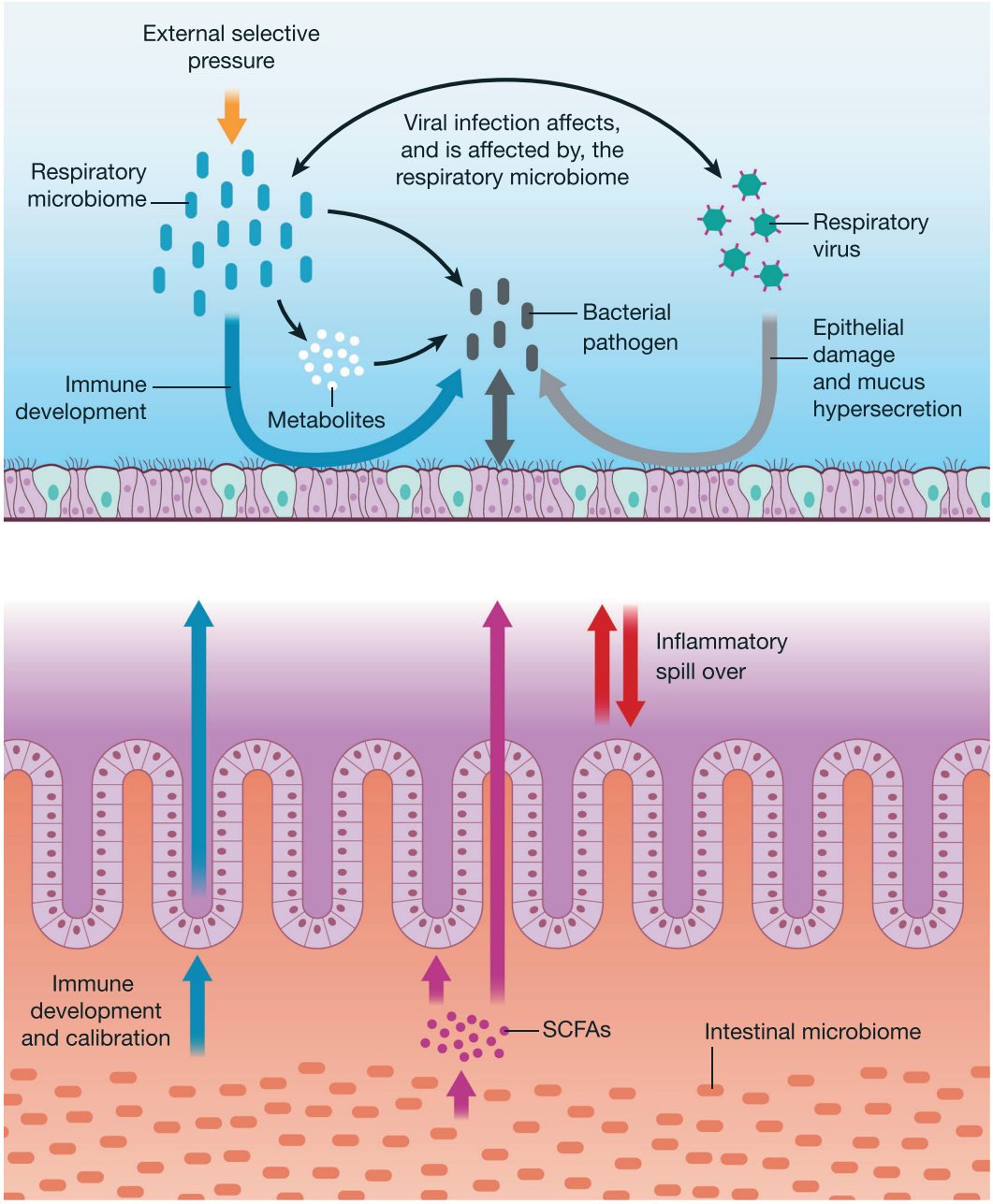

Fig. 2. Ways in which the host–microbe and microbe–microbe interactions influence acute and chronic respiratory bacterial infection. Top—Resident airway microbiome can directly (via bacterial interactions) or indirectly (via production of metabolite by-products) influence pathogen virulence. Respiratory microbiome is also associated with airway T-cell development. Respiratory viral infection can shift the respiratory microbiome, cause epithelial damage and induce mucus hypersecretion, altering respiratory bacterial infection susceptibility. External selective pressures such as antibiotics, physical airway obstruction or inhaled particles alter the respiratory microbiome. Bottom—Gastrointestinal microbiome directly assists in immune development and fine-tuning, influencing the respiratory immune response. Indirectly, the gastrointestinal microbiome, through production of short-chain fatty acids such as butyrate, promote colon epithelial health and exert broad anti-inflammatory activities, which influence lung immunity. Inflammation at either site can influence the other, a process termed inflammatory spill-over.

antibiotics, can trigger disruption of the gastrointestinal tract, either through the physiological effects of the drugs themselves, for example, the motor-stimulating activity of macrolide antibiotics (Itoh *et al*., 1984), or through the ablation of the gut microbiota (Bartlett, 2002).

Together, these studies show that the relationship between dysbiosis and respiratory inflammation is complex. It is likely to arise from a combination of loss of anti-inflammatory function, for instance, a reduction in SCFA production (Meijer *et al*., 2010; den Besten *et al*., 2013;

Trompette *et al*., 2014) and/or gain of proinflammatory function, such as an increase in the production of secondary bile acids (Duboc *et al*., 2013). As more mechanistic pathways are uncovered, their importance in correcting microbial dysbiosis in chronic diseases will become increasingly clear.

Many of the findings that support a gut-lung axis have been performed using germ free (GF) or antibiotic supplemented models. GF housing or antibiotic bacterial ablation, followed by microbiome transfer or cohousing with conventionally raised animals, provides a powerful tool to study the effect of a whole microbial community on host physiology. However, while mechanistic pathways link the gut microbiome to systemic immunity (Vangay *et al*., 2015), it is difficult to attribute physiological differences between GF/antibiotic-treated animals with conventional animals to a specific site, such as the gut, as bacterial communities on all sites are affected by GF housing or antibiotic treatment. While site-specific microbial ablation would be resolve this issue, it is technically challenging. Caution should also be taken when performing microbiome transfer experiments, as establishing a representative microbial community into GF animals takes several weeks to normalize with the mucosae (Johansson *et al*., 2015).

Conclusions and future directions

The potential for microbiome research to guide clinical diagnosis and treatment of infections and diseases is becoming better appreciated. The most utilized clinical practices to date, particularly for chronic LRT infections, are treatments that act to reduce pathogen burden, such as antibiotic therapies. Although, we know that these relatively blunt therapies are limited in their effectiveness and often lead to antibiotic resistance. As more mechanistic pathways highlighting host-microbe interactions emerge, the opportunities for targeted therapy increase. In both acute and chronic respiratory conditions, pathogens, which are the primary drivers of clinical prognosis, do not act in isolation, and both local and systemic interactions facilitate infection susceptibility and pathogenicity (Fig. 2). Integrating therapies that influence these underlying interactions, along with current treatments, may be a more effective treatment strategy.

In this review we have highlighted several potential strategies that could allow host–microbiota interactions to be exploited therapeutically. The URT microbiome is able to influence immunity, infection and disease susceptibility, both directly and indirectly; thus, supporting the data that demonstrate interventional strategies, such as probiotic nasal administration, is effective in some clinical scenarios. In addition, changing the mucosal environment, for instance through inhaled glycans, may impact on airway bacterial colonization dynamics via an altered metabolism and adherence profile, affecting infection susceptibility in both acute and chronic infection settings. The gut-lung axis has strong links with respiratory health, both in early life and in adults, which also present a possible point of intervention. Probiotic and prebiotic therapies that alter the gut microbiome have been shown to affect both acute and chronic respiratory conditions. In order to improve our limited capacity to manage chronic respiratory disease, we need to better understand the interactions between the microbiome and respiratory mucosa to identify more interaction pathways that can be targeted by novel strategies.

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