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SUPPLEMENT ARTICLE

Transkingdom Interactions Important for the Pathogenesis of Human Viruses

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The bacterial, fungal, and helminthic species that comprise the microbiome of the mammalian host have profound effects on health and disease. Pathogenic viruses must contend with the microbiome during infection and likely have evolved to exploit or evade the microbiome. Both direct interactions between the virions and the microbiota and immunomodulation and tissue remodeling caused by the microbiome alter viral pathogenesis in either host- or virus-beneficial ways. Recent insights from in vitro and murine models of viral pathogenesis have highlighted synergistic and antagonistic, direct and indirect interactions between the microbiome and pathogenic viruses. This review will focus on the transkingdom interactions between human gastrointestinal and respiratory viruses and the constituent microbiome of those tissues.

Keywords. immune response; influenza A virus; microbiome; respiratory syncytial virus; transkingdom.

The recent advances in metagenomic sequencing have revealed the complex interactions between host mucosal sites and their associated microbiota (viruses, bacteria, and fungi) and macrobiota (helminths). Microbiota are crucial for mucosal homeostasis and immunity [1], and perturbations of this balance between host and microbes are associated with dysfunction and disease [2]. The extent to which antibiotics can disrupt this balance and affect the ability of the host to combat pathogenic viral infections remains an active area of research. Although the interaction between bacteria and bacteriophage and also aspects of the human virome in preventing and promoting disease are of great interest, this review summarizes our current knowledge of how direct and indirect transkingdom interactions (Table 1) between the mucosal micro- and macrobiota and pathogenic viruses can shift the balance between factors that protect the host and those that promote the virus, with a particular focus on interactions in the gut and lung. Figure 1 summarizes the current state of knowledge on transkingdom interactions in the lung and gut.

ENTERIC BACTERIAL-VIRAL INTERACTIONS

Most of what is understood about transkingdom interactions has been derived from mouse models, which have yielded strong evidence of direct and indirect interactions between the gut microbiome and enteric viruses. In the early 1990s, it was observed that a nonpathogenic murine picornavirus could be rendered pathogenic if coadministered with lipopolysaccharides [3]. Since then, numerous landmark studies of enteric viruses have demonstrated that bacteria and/or bacterial products can promote virus stability (eg, that of reovirus [4] or poliovirus [4]), entry and/or attachment to target cells (eg, by norovirus [5] or poliovirus [6]), disease (eg, that caused by norovirus [7]), and persistence (eg, of retrovirus [8] or norovirus [5]). Murine norovirus, in an indirect interaction, takes advantage of bacterial suppression of interferon lambda (IFN-λ) to prevent viral clearance [9, 10]. It was recently shown that this interaction is region specific: virus in antibiotic-treated animals is reduced in the proximal small intestine but increased in distal sites [11]. It is interesting to note that the spatial effect was associated with bile acid priming of IFN-λ [11]. In another example of the intertwined host-bacteria-virus complexity, antibiotic treatment was shown to indirectly suppress murine astrovirus infection of goblet cells in vivo by decreasing mucus secretion, which is a process that is partially regulated by microbiota sensing and is also critical for astrovirus replication [12]. Adding to these complexities, closely related viruses such as poliovirus and coxsackievirus were shown to differ in their interactions with distinct microbiota based on varying antibiotic treatments, demonstrating even greater nuances in what are likely bacterial species-specific interactions with enteric viruses [13].

Given the numerous proviral effects afforded by direct and indirect interactions with commensal bacteria, antibiotics could be seen as a means to inhibit enteric viruses; however, this approach is likely to prove ineffective in clinical practice because the homeostatic deficits associated with microbiome disruption [14] could outweigh the antiviral effects. It is important to note that antibiotics can have bacteria-independent effects on virus infection. It was recently shown that antibiotic treatment in vitro can alter the plaque

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Table 1. Direct and Indirect Transkingdom Interactions Important to Viral Pathogenesis and Representative Examples

Mechanism		Virus	Organism(s)
Direct	Virion stability	IAV	GI bacteria, respiratory bacteria [43, 58]
	Innate immune response	Respiratory viruses	Helminths [45]
	Adaptive immune response	Respiratory viruses	Helminths [35, 63]
	Receptor availability	Herpesviruses	Bacteriophages [73]
Indirect	Cytokine production	Respiratory viruses	Respiratory bacteria [51]
	Microenvironment modulation	IAV	Aspergillus [64]
	Innate immune response	RSV	GI bacteria [54]
	Adaptive immune response	IAV	GI bacteria [57]
	Receptor availability	Rhinovirus	*Haemophilus* influenza [50]

Abbreviations: GI, gastrointestinal; IAV, influenza A virus; RSV, respiratory syncytial virus.

size of coxsackievirus and reovirus [15]. Although the mechanism of this alteration is unclear, these data indicate that the effects of using antibiotics in experimental models and, most likely, in clinical practice can extend beyond direct antimicrobial effects.

Commensal gut bacteria can protect against pathogenic bacteria and pathogenic viruses. Clinical trials of probiotic *Lactobacillus* spp and *Bifidobacterium* spp demonstrated efficacy against rotavirus [16]. The significance of these findings likely extends beyond rotavirus, because *Lactobacillus* spp were also found to inhibit transmissible gastroenteritis virus, a porcine coronavirus [17]. Although the precise mechanisms have yet to be elucidated, *Lactobacillus casei* and *Bacteroides thetaiotaomicron* can alter host glycoproteins, which results in decreased binding of rotavirus to target cells [18]. Bacterial flagellin can also play a role in rotavirus clearance via Toll-like receptor signaling that induces proinflammatory cytokines [19]. More recently, segmented filamentous bacteria were shown to block rotavirus infection by directly neutralizing the virus and promoting epithelial cell turnover [20]. Commensal organisms coevolve with the development of the intestinal immunity [21], particularly T-cell immunity that is critically important for the clearance of numerous enteric viruses [22–25]. Although the indirect actions of this immunity on enteric virus pathogenesis remain to be explored, a common feature across these studies is that promoting innate and adaptive immunity via commensal bacteria and probiotics may be a viable strategy for reducing viral pathogenesis in the gut. Additional studies to explore these possibilities are needed.

ENTERIC FUNGAL-VIRAL INTERACTIONS

Despite the estimated presence of more than 180 fungal species in the intestines of healthy individuals, there is a paucity of information detailing nonbacterial transkingdom interactions with the human gut mycobiome [26]. To date, only a handful of studies have examined the mycobiome during the progression of viral diseases. Decreased mycobiome diversity and increased prevalence of *Candida* spp were observed in the gut of patients with human immunodeficiency virus (HIV) [27]. In contrast, a correlative increase in gut fungal diversity was observed during hepatitis B progression [28]. However, these studies did not establish causative or directional relations between fungi and viral infection; thus, substantial evidence of a fungal role in viral pathogenesis in the human gut is lacking. The known interactions between fungi and enteric viruses, whether direct or indirect, are poorly characterized. The probiotic yeast *Saccharomyces boulardii* has demonstrated some efficacy as a therapeutic intervention against rotavirus-induced acute diarrhea, although the specific antiviral interactions have not been well defined [29]. Therefore, the nature of the interplay between viral pathogens and the enteric mycobiome remains unclear and requires further investigation. The rise of multidrug-resistant fungal pathogens lends urgency to this topic.

ENTERIC HELMINTHIC-VIRAL INTERACTIONS

Helminths that reside in the human gut, most commonly nematodes, cestodes, and trematodes, are frequently found in populations in low-income countries [30]. Helminths provoke complex immunomodulatory effects in the mammalian gut in response to infections [31] that are typically characterized by Th2-mediated responses effected via the interleukin (IL)-4Rα and STAT6 pathways and includes release of cytokines IL-4, IL-5, IL-9, and IL-13 [32, 33]. Consequently, helminth infection can induce immune responses that may not be appropriate for or effective at controlling viral infections. For example, diminished Th1 cytokine and $CD8^+$ cytotoxic T lymphocyte response during *Schistosoma mansoni* infection has been suggested to play a role in a decreased ability to fight viral infection during concurrent helminth infection [34]. Coinfection in mice with the nematodes *Trichinella spiralis* or *Heligmosomoides polygyrus bakeri* and murine norovirus resulted in a dampened $CD8^+$ T-cell antiviral response and higher viral loads in the murine intestine, compared with monoinfected control animals [35]. Furthermore, modulation of antiviral immunity could be observed in germ-free mice, indicating that these changes were independent of the resident bacterial microbiota. Infecting mice with *H polygyrus* or administering *S mansoni* eggs was found to reactivate latent murine gammaherpesvirus 68, which is similar to the human gammaherpesviruses (Epstein-Barr virus and Kaposi's

sarcoma-associated herpesvirus) [36]. Here, IL-4-induced activation of the Stat6 transcription factor promoted viral replication in conjunction with antagonism of IFN-γ-mediated viral suppression in response to helminthic infection [36].

In contrast, helminth infections may also provide a protective antiviral response due to the dynamic changes in immune response over the course of the infection. For example, the Th1-mediated parasite antigen response to migrating schistosomes in mice elicits an increase in IFN-γ, which suppressed hepatitis B virus replication [37]. In addition, Th2-mediated IL-4 release in response to *S mansoni* eggs augmented $CD8^+$ T-cell responses to murine herpesvirus 4, resulting in reduced viral disease severity [38]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic has raised discussion on the possible impact of helminth infection on coronavirus 2019 (COVID-19) disease severity. Some groups speculate that a concurrent helminth infection could negatively impact COVID-19 patients due to elevated Th2-associated cytokine levels. Others argue that a chronic helminth infection could benefit COVID-19 patients by reducing Th1-associated proinflammatory cytokines [39, 40]. Taken together, the results of these studies highlight that helminthic infections impacts viral pathogenesis. However, further studies are needed to evaluate the clinical significance of the contributions of helminths to viral infection.

PULMONARY BACTERIAL-VIRAL INTERACTIONS

Although the human upper and lower respiratory tract microbiomes are less well characterized than the gut, especially that of the healthy lung, transkingdom interactions are well described in both clinical practice and animal models. The best characterized of these interactions is the synergy between influenza A virus (IAV) and bacterial pathogens of the respiratory tract. Influenza A virus directly interacts with pathogenic constituents of the upper respiratory tract microbiome, including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [41, 42]. These interactions enhance bacterial pathogenesis [42] and alter immune responses to both *S pneumoniae* and IAV [41]. They can also alter IAV pathogenesis by promoting environmental survival and influencing transmissibility [43]. Infection with IAV causes lung cells to increase their expression of bacterial receptors [44], thereby enhancing bacterial adherence, and depletes alveolar macrophages [45], which are key to clearing bacterial infections in the lungs. Cytokines induced by IAV infection can exacerbate bacterial pneumonia caused by *S aureus* or *S pneumoniae* [46]. Likewise, respiratory syncytial virus (RSV) infection predisposes vulnerable populations to secondary bacterial pneumonia [47]. Direct interactions have been observed between RSV and both *S pneumoniae* and *H influenzae* [48], which can enhance bacterial and possibly viral pathogenesis [48].

The enhancement of respiratory viral pathogenesis by bacteria and bacterial products is due to direct and indirect mechanisms. Proteases released by bacteria or exposed on the bacterial surface enhance IAV pathogenesis by cleaving the viral hemagglutinin to enable receptor binding [49]. Preincubation of epithelial cells with *H influenzae* promotes the adherence of

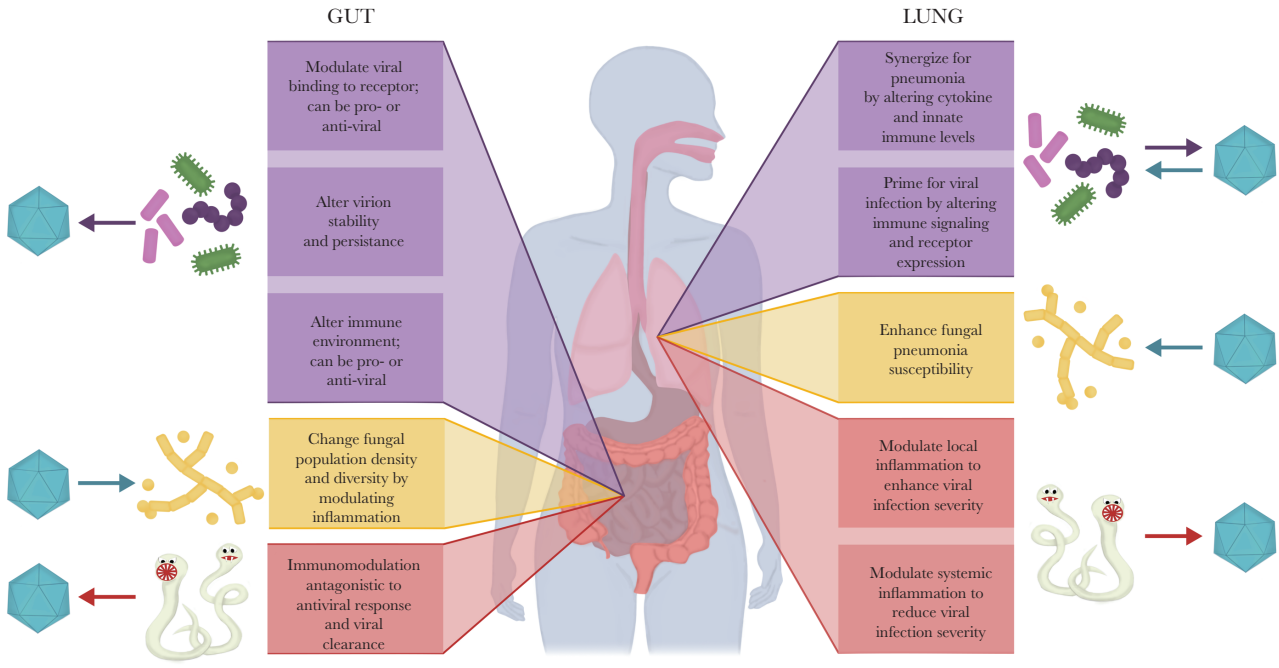

Figure 1. Summary of transkingdom interactions in the lung and gut. Interaction between viruses and bacterial, fungal, and helminthic components (top to bottom) of the microbiome. Arrows indicate primary direction of interaction between the virus and the component of the microbiome.

rhinovirus to the cells through increased expression of intercellular adhesion molecule (ICAM)-1 and enhances the pathogenesis of rhinovirus infection through upregulation of TLR3 and subsequent proinflammatory cytokine production [50]. These interactions do not require viable bacteria because heat-killed *H influenzae* also increased ICAM-1 expression, viral replication, and proinflammatory cytokine production when used to coinfect cells along with rhinovirus or RSV [51]. The enhancement of respiratory viral pathogenesis by bacterial products extends to heat-killed *Pseudomonas aeruginosa*, adenovirus, and influenza B virus, but not to heat-killed *S pneumoniae* [51], suggesting that the respiratory bacterial community exerts species-specific effects on viral pathogenesis. Insights into which bacterial communities in the upper and lower respiratory tract are proviral or antiviral could help stratify populations according to their risk of pneumonia and inform antibiotic treatments to spare antiviral commensal bacteria.

Finally, in the "gut-lung axis," the bacterial gut microbiome can alter the response to respiratory infection [52] and viral upper respiratory infection can alter the bacterial gut microbiome [53]. Gut microbiome-derived compounds alter IFN signaling in the lungs, thereby conferring protection against RSV [54] and IAV [52] in murine models. In human transplant patients, the presence of butyrate-producing bacteria in the gut reduced the incidence of lower respiratory tract viral infection after bone marrow or kidney transplant [55, 56]. Together, these data support the immunomodulatory roles of the gut microbial community in regulating respiratory immune response and susceptibility to respiratory viral infection, even in the context of immunosuppressive posttransplant medication. The enteric community alters both cell-based and humoral responses to IAV [57]. Bacterial products found and made in the gut community can also destabilize respiratory viruses, including IAV [58] and coronaviruses [59], which suggests that there is a mechanism for tissue tropism and modulation of environmental stability. These findings, taken together, suggest the diverse roles played by the microbiota in the enteric and respiratory tracts in terms of modulating both the risk of acquisition and the severity of viral infection in healthy and high-risk hosts.

PULMONARY VIRAL-HELMINTH INTERACTIONS

When viruses and parasites coinfect a host, one infectious agent can skew the immune response away from the natural response to the other invader, even if the 2 agents are infecting distinct sites within the host, as in the "gut-lung axis." In the case of viruses that cause immunopathologic disease, such as IAV and RSV, such interactions can be beneficial to the host. Coinfection with *Trichinella spiralis* and IAV causes a reduction in both tumor necrosis factor-α production and immune-cell infiltration into the lungs after IAV infection, leading to a quicker recovery [60]. *Heligmosomoides polygyrus* coinfection with IAV results in decreased viral loads and correspondingly decreased hemagglutination inhibition titers [61]. Likewise, *H polygyrus* coinfection with RSV results in decreased viral loads and reduced pulmonary inflammation [62]. More importantly, neither of these eukaryotic parasites have pulmonary stages in their life cycles; therefore, they apparently act remotely to modulate the immune microenvironment in the lung during viral infection.

More complex interactions occur when viruses and parasites both directly infect the lungs. *Nippostrongylus brasiliensis* infection leads to increased IAV lung titers, but only when larvae are actively migrating through the lungs. In contrast, quiescent parasites can induce proinflammatory states that are protective against secondary viral infection. *Schistosoma mansoni* oviposition results in granulatomous inflammation in the lung that can protect against secondary infection with IAV or pneumovirus [63]. These interactions, taken together, demonstrate that the multivariate nature of virus-parasite interactions in the lung is dependent on the species of virus and parasite, the life stage of the parasite, and the site of the parasite infection. As with enteric helminth infection, a better understanding of helminth-virus interactions will have particular benefit for global health and especially in low-income countries, where upper respiratory viruses are a leading cause of pediatric mortality.

PULMONARY VIRAL-FUNGAL INTERACTIONS

Emerging evidence suggests that fungi play important roles in viral pathogenesis in the lungs. Multiple case reports suggest that after influenza virus infection, immunocompetent patients can become infected with *Aspergillus* [64]. It is hypothesized that the lung microenvironment during and after influenza virus infection predisposes the lungs to *Aspergillus* infection. Treating influenza with steroids and/or neuraminidase inhibitors can further increase the risk of secondary fungal infections [64, 65]. In humans, pulmonary fungal infections are predominately associated with immunosuppressive disorders such as HIV infection. Fungal infections in patients with HIV infection are primarily caused by members of the *Aspergillus*, *Cryptococcus*, and *Pneumocystis* genera [66] and are one marker of progression to acquired immune deficiency syndrome. The immunosuppressive state induced by HIV infection enables the colonization of the lung by these opportunistic and environmental fungi. Human immunodeficiency virus and another immunosuppressive virus, measles virus, both trigger "vomocytosis," which causes the expulsion of *Cryptococcus* cells from virally infected macrophages, potentially exacerbating disease severity and spread [67].

PATHOGENIC VIRUS-BACTERIOPHAGE INTERACTIONS

Bacteriophages are important components of the microbiome. They are primarily known for their role in intestinal homeostasis, immune tolerance, and mucosal immunity [68].

Bacteriophages that parasitize the bacterial population of the lung have been described in (1) healthy lungs [69], (2) lungs with chronic obstructive pulmonary disease [69], and (3) lungs with cystic fibrosis [70]. It is interesting to note that these bacteriophage communities can be diverse even within the same patient [70]. Bacteriophages encode virulence and antibiotic resistance genes [69–71]; therefore, antibiotic therapies that activate lysogenic bacteriophages risk causing the spread of bacterial virulence factors and, more importantly, contribute to the rise of antimicrobial resistance. Although bacteriophages primarily exert indirect effects on viral pathogenesis through their regulation of the microbiome, they have been shown to have more direct interactions with viral pathogens. Bacteriophages contain many of the pathogen-associated molecular patterns (PAMPs) that are common to pathogenic viruses and that can stimulate host immune responses. These PAMPs include bacteriophage nucleic acids, which can stimulate IFN production and predispose the host to mount an antiviral immune response [72]. In addition, bacteriophages can directly inhibit pathogenic viruses by competing with them in binding to receptors. This has been demonstrated for several viruses, particular herpesviruses, which can be outcompeted by bacteriophages in binding to their receptor [73]. Bacteriophage therapy, the use of bacteriophages to therapeutically kill bacteria, has been explored since the early 1900s and shows promise against the superbugs of today [74]. Future studies should consider the role of bacteriophages and bacteriophage therapy in viral pathogenesis.

CONCLUSIONS

The direct and indirect interactions between viruses and the micro-, myco-, and macrobiomes of the lung and the gut represent an important and growing area of research. These studies are providing fundamental knowledge about the importance of transkingdom interactions in health and disease, and they may identify new therapeutic targets for viral infections. The enhancement of the infectivity of viruses by direct interactions with bacteria, fungi, or macrobiota can have significant consequences beyond those highlighted here, including increasing the effective multiplicity of infection and enabling complementation of defective viral particles. Therefore, understanding the impact of coinfecting pathogens and of the symbiotic microbial communities on viral pathogenesis and on immune responses will inform antibiotic choices and vaccine design to take advantage of host-beneficial interactions and minimize viral-beneficial interactions. Moreover, the implementation of bacteriophage therapy and the use of precision antibiotics that are designed to spare commensal bacteria will be key advances but might also have unforeseen consequences for infections with pathogenic viruses. These observations underscore the importance of understanding the complex microbial community encountered by pathogenic viruses and the synergistic and antagonistic interactions that occur therein.

Notes

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