Microbiota and Its Role on Viral Evasion: Is It With Us or Against Us?

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Viruses are obligate intracellular pathogens that require the protein synthesis machinery of the host cells to replicate. These microorganisms have evolved mechanisms to avoid detection from the host immune innate and adaptive response, which are known as viral evasion mechanisms. Viruses enter the host through skin and mucosal surfaces that happen to be colonized by communities of thousands of microorganisms collectively known as the commensal microbiota, where bacteria have a role in the modulation of the immune system and maintaining homeostasis. These bacteria are necessary for the development of the immune system and to prevent the adhesion and colonization of bacterial pathogens and parasites. However, the interactions between the commensal microbiota and viruses are not clear. The microbiota could confer protection against viral infection by priming the immune response to avoid infection, with some bacterial species being required to increase the antiviral response. On the other hand, it could also help to promote viral evasion of certain viruses by direct and indirect mechanisms, with the presence of the microbiota increasing infection and viruses using LPS and surface polysaccharides from bacteria to trigger immunosuppressive pathways. In this work, we reviewed the interaction between the microbiota and viruses to prevent their entry into host cells or to help them to evade the host antiviral immunity. This review is focused on the influence of the commensal microbiota in the viruses’ success or failure of the host cells infection.

Keywords: microbiota, microbiota-virome interaction, microbiota and antiviral immune defense

INTRODUCTION

The mucosal surfaces of the human body contain complex communities of microorganisms collectively referred to as microbiota; these bacteria are a key factor in health and disease due to their participation in the development of the immune system and their host-protection against pathogens (Human Microbiome Project Consortium, 2012a,b; Lloyd-Price et al., 2016).

Viruses are a large and heterogeneous group of dependent biological agents that require the host-cell machinery to replicate. Most viruses are identified based on their capacity and mechanisms used to produce disease; however, healthy individuals harbor viral communities that do not cause directly known pathologies. These viral communities are known as the human virome (Rohwer et al., 2009). The coexistence of viruses and bacteria within the microbiome encourages the study of viral evasion mechanisms that provide immune system tolerance to these pathogens. These

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mechanisms are undoubtedly also used during the pathophysiology of viral diseases (Abeles and Pride, 2014).

**MICROBIOTA AGAINST VIRAL INFECTION**

Since the discovery that gut bacteria instruct host immunity, i.e., they restrict pathogen proliferation, it would seem logical to think that the intestinal microbiota would also play a predominant role in viral etiology infection inhibition. Studies reveal that commensal bacteria are crucial in maintaining immune homeostasis and immune responses at mucosal surfaces (Ichinohe et al., 2011). Mucous membranes are the gateway to many pathogens, including viruses. For example, intestinal microorganisms promote maturation of the secondary lymphoid organs within the gastrointestinal tract, which is the first line of defense of the intestinal mucosa (Karst, 2016). Germ-free mice are unable to mount an efficient immune response against pathogens due to immature intestinal lymphoid structures (Hooper et al., 2012; Kamada and Núñez, 2014).

Given the complexity of the microenvironment in mucosal surfaces, it makes sense that the most studied bacteria and virus interactions are the ones involving the intestinal microbiome. The protective role of commensal bacteria, mainly probiotics, is well-established; however, in its interactions with viruses, more studies are needed. The *Lactobacillus* genus can inhibit murine norovirus (MNV) replication *in vitro*, which could be mediated by the increased expression of IFNβ and IFNy. *In vivo* models show that these bacteria are decreased during MNV infection, though with the aid of retinoic acid treatment, it is possible to avoid this effect. It has been hypothesized that the antiviral effects of vitamin A (and consequently, retinoic acid) are mediated by the *Lactobacillus* genus due to interferon production (Lee and Ko, 2016).

Bacterial flagellin is efficient against rotavirus (RV) infection because it activates Pattern Recognition Receptors (PRR), TLR5 and NLRC-4, that stimulate the release of interleukin-22 (IL-22) and IL-18; the former induces normal epithelium proliferation, and NLRC-4, that stimulate the release of interleukin-22 (IL-22) because it activates Pattern Recognition Receptors (PRR), TLR5 of defense of the intestinal mucosa (Ichinohe et al., 2011; Wilks and Golovkina, 2012). The commensal gut microbiota regulates the respiratory mucosa immunity against respiratory influenza virus through the IgA secretion, and the proper activation of inflammasomes, Th1 cells, and CTLs, and through the upregulation of TLR7 signaling in the respiratory mucosa (Ichinohe et al., 2011; Wu et al., 2013). Steed et al. (2017) demonstrated that desaminotyrosine, a microbial metabolite, enhances type 1 interferon (IFN-I) signaling and protects against influenza pathogenesis.

Gut probiotics like *Lactobacillus paracasei* and *Lactobacillus plantarum* increase pro-inflammatory cytokines like IL-33, IL-1α, IL-β, IL-12, and IFNy during influenza virus infection. There is also an increase in the presence of innate immune cells in the lungs such as NKS, macrophages, and dendritic cells. These probiotics were also able to diminish the inflammatory response in the lungs by an IL-10 increase, thereby controlling the antiviral response (Park et al., 2013; Belkacem et al., 2017). The crosstalk between the gut and airway bacteria through the gut-lung axis could explain how the intestinal bacteria are able to improve antiviral immunity since gut microbial metabolites could stimulate immune cells that can move to distal locations to mediate the antiviral response.

On the respiratory surface, airway bacteria protect against viral infections. *Staphylococcus aureus* stimulates the recruitment of peripheral CCR2+ CD11b+ monocytes and their subsequent maturation into M2 macrophages, through the activation of TLR2 signaling during influenza infection. This mechanism dampens influenza-mediated acute lung injury (Wang et al., 2013). The respiratory commensal bacteria, *Corynebacterium pseudodiphtheriticum* modulates the TLR3 antiviral response against Respiratory Syncytial Virus (RSV), enhancing the production of TNFα, IL-6, IFNy, and IFNβ through the increase of T-cell subpopulations that produce these cytokines (Kanmani et al., 2017).

The vaginal mucosa is dominated by bacteria from the *Lactobacillus* genus. Vaginal microbial communities dominated by *Lactobacillus crispatus* were associated with a decreased HIV infection in South African women (Gosmann et al., 2017). *L. crispatus*, *Lactobacillus gasseri*, and *Lactobacillus vaginalis* inhibit HIV-1 replication in *ex vivo* cervico-vaginal tissue culture. These effects are mediated through acidification of the medium and lactic acid production, as well as their binding to the virus in order to reduce the free virions in the tissue (Nahui Palomino et al., 2017). Lactic acid and acidic pH increase the production of anti-inflammatory cytokines, preventing the production of pro-inflammatory cytokines by epithelial cells and, with this, the inflammation that increases HIV acquisition (Hearps et al., 2017). Lack of the vaginal microbiome by antibiotic depletion leads to IL-33 increased production which suppresses IFNy secretion, leading to Herpes Simplex Virus type 2 (HSV-2) susceptibility due to an impaired antiviral defense (Oh et al., 2016).

These findings demonstrate that commensal bacteria in different mucosal sites are part of the antiviral response against
pathogenic viruses; nevertheless, there is much yet to define in the mechanisms through which they can achieve this (Figure 1A).

**MICROBIOTA AS PROMOTERS OF VIRAL INFECTIONS**

Despite the significant evidence available about the role of the microbiota in the regulation of the mucosal immune system and the host protection from viral infections, it is also known that, through microbiota rich mucosal surfaces, different viruses enter host cells most efficiently. Furthermore, viruses escape the immune response to establish chronic infections. Then, contrary to the known benefits of gut microbiota, intestinal viruses take advantage of gut bacteria to trigger replication at favorable transmission sites (Kuss et al., 2011).

Human and murine norovirus (MNV) require the presence of bacteria to infect B cells since the lack of both bacteria by antibiotic treatment and B cells in Rag-/- mice inhibit the infection by norovirus (Jones et al., 2014; Baldridge et al., 2015). MNV also targets intestinal tuft cells by the CD3001f receptor and antibiotics reduce the specific genes for these cells in the colon. The MNV needs the colonic commensal microbiota to regulate these epithelial cells to utilize them as a reservoir for its chronic infection (Wilen et al., 2018). Commensal bacteria from the human gut, such as *Enterobacter faecium*, *Klebsiella* spp., *Bacillus* spp., *Bacteroides thetaiotaomicron*, *L. plantarum*, and *L. gasseri*, among others, bind human norovirus through bacterial pili and membranes, possibly through HBGA-like (histo-blood group antigens) molecules, sialylated gangliosides, and lipopolysaccharides (LPS), which can facilitate the entry of these viruses and the development of the infection (Almand et al., 2017). It is yet to be elucidated the exact mechanisms and molecules this virus utilizes to bind on bacterial surfaces; however, these interactions are a good example of viruses exploiting commensal bacterial to promote their infectivity (Figure 1B).

The intestinal microbiota enhances mouse mammary tumor virus (MMTV), poliovirus, and mammalian orthoreovirus (reovirus) infections (Kane et al., 2011; Kuss et al., 2011). MMTV
VIRUSES AS PART OF THE HUMAN MICROBIOME

The intestine contains other types of organisms, besides bacteria, that can influence mucosal and systemic immune responses such as viruses (Minot et al., 2012; Kernbauer et al., 2014; Norman et al., 2015). To interpret the role of the microbiota within viral infections, we must also consider the impact that the virome may play in this interaction. A recent study approximated that in healthy humans, there are 45% of mammalian viruses that are part of the virome without a clinical outcome (Rascovan et al., 2016; Olival et al., 2017). However, similar to bacteria, resident viruses modulate the immune responses (Freer et al., 2018).

Enteric human virome has also been linked to diseases. For example, enteric eukaryotic viruses can be associated with gastroenteritis, enteritis, or colitis (Norman et al., 2015). Bacteriophages perturb the bacterial community, interplay with the host immune system, and an antagonistic relationship between bacteria and bacteriophages during inflammatory bowel disease has been reported (Duerkop and Hooper, 2013; Virgin, 2015). Also, bacteriophages contribute to the spread of antibiotic resistance genes among bacteria; they form a reservoir of these genes within the microbiome (Muniesa et al., 2013; Quiros et al., 2014). In Crohn’s disease, a reduction in viral diversity is part of its characteristic dysbiosis (Abeles and Pride, 2014).

Changes in the intestinal virome are significant in AIDS and HIV enteric disease pathogenesis. Reciprocal transactivation between HIV-1 and other human viruses have been reported (White et al., 2006). Monaco et al. found a relation between the enteric adenovirus sequence expansion and the advanced HIV/AIDS stage (Monaco et al., 2016). Also, AIDS alters the commensal plasma virome since an increase in the proportion of anelloviruses has been reported (Li et al., 2013). In this study, the presence of viral sequences from HIV, HCV, hepatitis B virus (HBV), human endogenous retroviruses (HERV), and GB virus C (GBV-C) in the plasma virome of HIV subjects was also found. HSV-2 may alter vaginal epithelial integrity, which favors HIV infection and transmission (Shannon et al., 2017). Furthermore, it induces genital inflammation and, in the genital tract mucosa, it increases HIV susceptible target cells (Rebbapragada et al., 2007). Epidemiological studies report a coincidence in different populations of women who have a high incidence of HSV-2 infection and an increased HIV risk (Shannon et al., 2017). Viral-bacterial interactions involving HSV, human cytomegalovirus (HCMV), and Epstein-Barr virus type 1 (EBV-1) might contribute to the development of periodontitis, since HSV infects T-lymphocytes and monocytes/macrophages, EBV-1 infects B-lymphocytes, and HCMV infects monocytes/macrophages and T-lymphocytes, which may cause an impaired immune response against bacteria (Contreras and Slots, 2003; Elamin et al., 2017). HSV may promote subgingival attachment and colonization by periodontopathic bacteria using the capsid proteins as receptors for bacteria (Bakaletz, 1995; Contreras and Slots, 2003). This is similar to one of the mechanisms by which commensal bacteria collaborate with viral infections. Chronic periodontitis has also been related to the natural history of HPV in patients with base of tongue cancers (Tezal et al., 2009), since it facilitates the life cycle of HPV infection in the periodontal pocket (Shipilova et al., 2017). This represents a clear example of a virus-bacteria-virus interaction that ends in
increased susceptibility to the disease, in this case, head and neck cancer.

**LIMITATIONS OF STUDIES EVALUATING BACTERIA-VIRUSES’ INTERACTIONS**

It was supposed that bacteria removal, by antibiotics or the lack of these microorganisms in germ-free models, would increase the predisposition to viral infections; on the other hand, it was found that microbiota ablation decreases the infectivity of pathogenic viruses. Experimental systems to evaluate the role of the gut microbiota during enteric viral diseases included two strategies: the infection of germ-free mice and the administration of treatments to eliminate the commensal microbiota in mice prior to a viral infection (Karst, 2016). However, there are several problems with germ-free animals, such as defects in mucosal immune development and changes in intestinal morphology, while the antibiotic treatment has some disadvantages—antibiotics do not remove the entirety of the commensal microorganisms (Wilks and Golovkina, 2012), some gut species are unculturable so its complete absence can’t be proved (Schmeisser et al., 2007), there is currently evidence of antimicrobial resistance of some bacterial groups (Pogue et al., 2015).

The study of the effects of the intestinal microbiota on the host immune system requires precisely defined experimental approaches that are complex, and the requirement of samples limits in vivo analysis. Also, the study of the microbiome suggests that there is significant variability among individuals, this indicates that microbiomes are dynamic “fingerprints”, though they can change depending on environmental challenges (Bogdanos et al., 2015).

Improvement of in vitro and ex vivo cultures to simulate more accurately the in vivo conditions of microbiome-virome interactions is needed to be able to understand the complexity of this relationship. Otherwise, these models are too simplistic in their approaches, and they should only be used as a first encounter in order to further elucidate the mechanisms of these relations. “Ommics” approaches are essential methods to unravel these interactions since pathogenic viruses not only interact with one type of bacteria, but with hundreds of them. Further studies of the relationship between these microorganisms need to take into consideration these approaches to improve our understanding of the complexity of mucosal surface microenvironments.

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