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Virus and microbiota relationships in humans and other mammals: An evolutionary view

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ABSTRACT

In the last decades, studies have revealed multiple and strong correlations between the host and its commensal microbiota consisting of bacteria, protozoa, fungi and viruses. This associated microbiota can positively or negatively influence the course of a wide range of infections. Here, we review the interactions between the host and its viral microbiota and discuss new paradigms from an evolutionary perspective. The viral adaptation to a microbial environment in a co-evolutionary approach is highlighted, as well as viral cross transmission in the context of the barriers imposed by the indigenous microbiota. In addition to reviewing the host-microbiota-virus relationships, we focus the discussion on microbiota-virus interactions that could be applied to preventive and therapeutic treatments.

1. Introduction

Viruses are the most abundant biological entities on Earth and have evolved with prokaryotes and eukaryotes for thousands of years. The abundance of viruses varies according to the environment and sometimes is relative to bacterial activity and colonization [1]. The human gut harbors a dense and complex microbial ecosystem, with presents not only prokaryotic and eukaryotic organisms but also viruses (virobiota, and their genes – virome). This indigenous microbiota can be associated with the host cells (eukaryotic virobiota) or with some of the approximately 2776 prokaryotic species that inhabit it (prokaryotic virobiota) and this interation may be beneficial or detrimental to the host [2]. An example of a positive effect is the adherence of phages to mucus forming an antimicrobial barrier in various host mucosal surfaces [3]. This co-evolutionary mechanism is called “non-host-derived immunity” and acts primarily controlling the abundance and equilibrium of bacterial populations [3,4]. The evolutionary battle between viruses and prokaryotes was reported in the last years by studies on the “Kill the Winner” hypothesis, horizontal genetic exchange, CRISPR-encoding bacteria and viral anti-CRISPR proteins [5–7]. Investigation of these relationships has provided important biotechnological tools that can be used for genetic engineering such as CRISPR-Cas9 genome editing human cells [6].

Recent studies have shown that the host’s normal microbiota is able to influence the infections caused by various families of animal viruses [8–10]. Microbiota-virus interactions have been studied in germ-free mice or antibiotic-treated mice models highlighting the opposing modulating effects of commensal bacteria on the course of viral infections [9,10]. Commensal bacteria can potentially influence viral infections either hindering or promoting the viral infection and sometimes aggravate the disease [8,9]. Bacteria commonly isolates from human nasopharynx as *Staphylococcus aureus*, *Pseudomonas* species, *Streptococcus pneumonia*, *Haemophilus influenzae* and *Streptococcus pyogenes* has been associated with increased risk of death in adults and children infected with influenza [11].

This review highlights the important role of microbiota-virus interactions through an evolutionary perspective, emphasizing the viral adaptations to the microbial environment and the use of available resources by viruses. The cooperation or the competition with other components of the indigenous microbiota, as well as the co-evolution with host and viral cross-species transmission in the context of the barriers imposed by the endogenous microbiota are also addressed.

2. Viruses versus microbial ecosystem

Viral particles face numerous host-related challenges to reach the

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permissive cells, such as tissue specificities, body temperature and epithelial secretions including IgA, defensins and a mucus barrier, as well as environmental modifications due to microbiota metabolism and cellular composition such as pH, redox potential, lipopolysaccharide (LPS) and glycans. The gastrointestinal microbiota is the most complex and diverse ecosystem in mammals, quite different when compared to those present in other body sites, and there is a considerable variation in the constituents of the gut microbiota among apparently healthy individuals [12].

The presence of the microbiota or its products is associated with increases in the viral fitness for all enteric viruses studied so far, including *Enterovirus C* (poliovirus) [13,14], *Mammalian reovirus* [13], *Rotavirus* A [15], *Norwalk virus* (norovirus) [16–19] and *Mouse mammary tumor virus* (MMTV) [20,21] (an enteric retrovirus). In this context, some findings suggest different mechanisms by which the enteric viruses could use bacteria and their products to withstand environmental adversities and cross the host cell barriers.

A study of poliovirus was the first to show that viral exposure to bacteria enhanced host cell binding and infection by the virus [13]. The enhancement of viral infectivity did not require live bacteria, and the presence of bacterial surface polysaccharides, including LPS and peptidoglycan (PGN), was sufficient [13]. LPS is the major cell wall component of Gram-negative bacteria with highest concentrations in the gut lumen [22]. Poliovirus can use LPS to promote attachment to the surface of permissive cells through direct facilitation of viral binding to its poliovirus receptor (Fig. 1A). In addition, LPS can enhance virion environmental stability by increasing its thermostability and resistance to chlorine bleach [13,14]. A specific residue in the capsid protein of poliovirus VP1 was shown to be crucial for stabilization, and this ability is important to prevent premature conformational changes before uncoating [14] (Fig. 1B). A mechanism similar to the LPS-mediated stimulation of poliovirus was observed for human norovirus when it was discovered that it could infect human B cells [16]. Some specific commensal bacteria express a glycan called histo-blood group antigen (HBGA) that correlated with the ability of norovirus to attach and infect B cells [18]. The isolated HBGA was sufficient to stimulate viral attachment to the surface of B cells [19] (Fig. 1C) by using a mechanism apparently very similar to that of poliovirus-LPS attachment to its host receptor. However, the receptor used by human norovirus remains unknown precluding an understanding of the mechanism by which bacterial HBGA stimulates viral attachment [19].

It is not yet clear how viruses cross all of the barriers to reach the host cells, such as those which separate virus from B cells and the human norovirus-HBGA complex located in the intestinal lumen. Some opportunistic members of the commensal microbiota contribute to the process of injury of the gut barriers by primarily destroying the mucus layer or even the enterocytes by using the enzymatic apparatus [23]; viral particles could use these passages to reach the target cells. Furthermore, many bacteria can translocate, which is the ability to pass through the intestinal epithelium from the lumen to the internal compartment [24].Viruses may adhere to bacterial surfaces during translocation, which occurs through the transcellular (inside enterocytes) or the paracellular (by passing through the intercellular space between the cells) pathways. This phenomenon described here as “microbial phoresy” is defined in ecology as an inter-species biological interaction where an organism is mechanically transported by its host. Phoresy is frequently used within the animal kingdom and is a type of commensalism where neither organism is physiologically dependent on the other. Recently, the binding of human norovirus around the outer cell surfaces and pili structures of bacteria was described, but without apparent localization [25] (Fig. 1D). A similar function may be present in other viruses of different viral families seen the affinities between these and bacterial surface components [26]. In conclusion, viruses can interact with the microbiota and their products to increase viral fitness through virion stability and enhanced binding to the surface of target host cells. (Fig. 1A–D).

3. Host immune environment: From tolerance to battlefield

The intestinal microbiota interacts with the whole host immune system and consequently with antiviral immune responses. However some viruses have evolved to use this phenomenon, the microbiota being directly involved in viral evasion of the host immune system and in induction of a tolerogenic microenvironment. The establishment of a tolerogenic microenvironment is made by specific regulatory T cells, highly prevalent in the intestine and responsible for recognition of commensal microbiota and for the immunological tolerance to many of its non-pathogenic components [27].Viruses may use regulatory T cells to influence antiviral immune responses, such as for the persistence of MMTV retrovirus infection in mice pups (Fig. 2). MMTV seems to bind directly to LPS and then incorporates LPS-binding host proteins into its envelope, such as CD14, MD2 and TLR4. Virions isolated from knockout mice for LPS-binding proteins were unable to bind to LPS [20,21]. It is important to highlight the immunostimulatory nature of LPS in generating sequential events in which binding of LPS to TLR4 drives the production of IL-6, which then induces IL-10 secretion [20,21] (Fig. 2). In addition, virion-LPS binding is essential for viral transmission in pups that ingested MMTV-laden maternal milk [20]. Furthermore, infected mouse pups failed to produce detectable antiviral antibodies when immunized orally with viral antigens, whereas those which were exposed to MMTV intraperitoneally were not tolerant to MMTV antigens [20]. These data revealed that interactions between the microbiota and MMTV promotes tolerance to viral antigens and facilitates the establishment of a persistent viral infection.

Another virus that has been shown to benefit from the bacterial modulation of the host immune system is murine norovirus (MNV), which presents a bacteria-mediated persistence [28]. In vivo assays using mice treated with antibiotics for bacterial depletion showed that the treatment inhibits persistent MNV infection in the intestine [28]. The tissue infection and systemic viral replication were not affected by antibiotic's treatment and the persistent infection occurred only when the microbiota was recomposed [28]. Additionally, mice lacking IFN-λ receptor were persistently infected with a MNV irrespective of the presence of commensal microorganisms [28,29]. The hypothesis currently accepted is that commensal bacteria suppress the production of IFN-λ upon their interaction with MNV [28,29]. Similarly, this cytokine also controls rotavirus infection in murine model [30]. However, a study showed that MNV can replace the beneficial function of microbiota in germ-free or antibiotic-treated mice restored intestinal morphology and lymphocyte function without inducing overt inflammation and disease [31]. The IFN-α receptor was associated with the ability of MNV to compensate for bacterial depletion and kept the intestinal homeostasis [31].

As pointed out above, the modulation of the immune system by the microbiota can promote viral infection, but can inversely benefit the host depending on the viral agent. The presence of the microbiota is essential for an effective immune response against the *Vaccinia virus* (VACV), a large and complex enveloped virus belonging to the *Poxviridae* family [32]. An *in vivo* study demonstrated that VACV presented a similar profile of systemic infection in germ-free and immunosuppressed mice models, whereas conventional mice were refractory to this infection [32]. Additional *in vivo* studies have also demonstrated a microbiota-mediated protection against the *Influenza A virus,* in which the microbiota activated the inflammasome [33]. The inflammasome activation induced migration of dendritic cells from the lung to the draining lymph node, to stimulate influenza-specific T-cell responses (Fig. 3A). Antibiotic treatment in mice caused microbiota depletion and increased the animals’ susceptibility to the virus [34]. Additionally, recent studies highlighted the importance of signals derived from commensal bacteria that can calibrate the activation threshold of innate immunity, and revealed an interplay between commensal and antiviral interferon signaling pathways in macrophages, involved in responses to *Influenza A virus* [35]. Conversely,

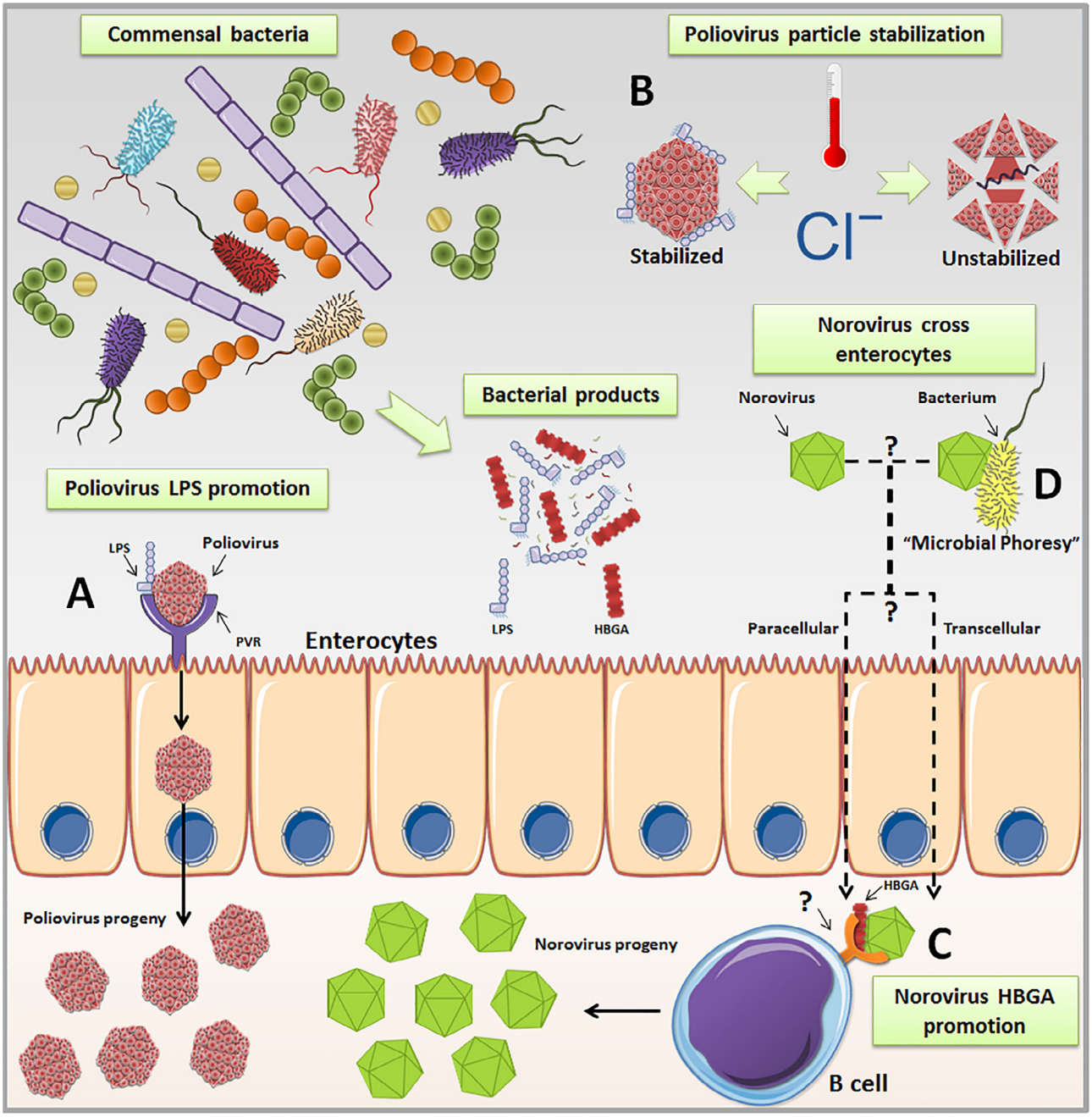

Fig. 1. Representative mechanisms by which bacteria and their products are used by viruses to cross the barriers to the host's cells and increase viral fitness. (A) Viral exposure to bacterial products enhanced binding to the host cell and infection caused by poliovirus. (B) Association of poliovirus particles with LPS increases their thermostability and resistance to inactivation by chlorine bleach. (C) HBGA-mediated stimulation mechanism used by norovirus to infect human B cells. (D) A commensal bacterium contributing to the ability of norovirus to cross all of the barriers to the host cells by the "microbial phoresy" mechanism.

studies also showed that respiratory influenza infection could cause digestive diseases such as intestinal immune injury and secondary infections in gut [36,37]. The intestinal immune injury may have resulted from an altered intestinal microbiota composition mediated by IFN-γ produced by lung-derived T-cells and recruited into the intestine (Fig. 3B) [36].

Therefore, in the host immune system environment, the cross-talk between microbiota and virus shows a two-way pattern involving regulator and regulated agents, both the microbiome and the viral infection having had alterations in their composition and fitness, respectively. In summary, the triangular relationships between viruses, microbiota and immune system are complex and vary from tolerance to dysbiosis in a phenomenon shaped by co-evolution.

4. From co-evolution to cross species transmission

In host-microbiota-virus co-evolution, each element of this relationship exerts selective pressures the others, thereby affecting the evolutionary aspects in general. Many organisms have been described for their probiotic effect on various types of viral infections, leading to consequent applications in preventive and therapeutic approaches [38–41]. Specific members of the microbiota may have a promoter or inhibitory effect on viral infections in the original or new host.

The human female vaginal microbiota co-evolved with the entire genus *Lactobacillus* [42]. These bacteria responsible for production of antiviral agents such as hydrogen peroxide (H_2O_2) and lactic acid are dominant in the vaginal ecosystem. The hydrogen peroxide produced

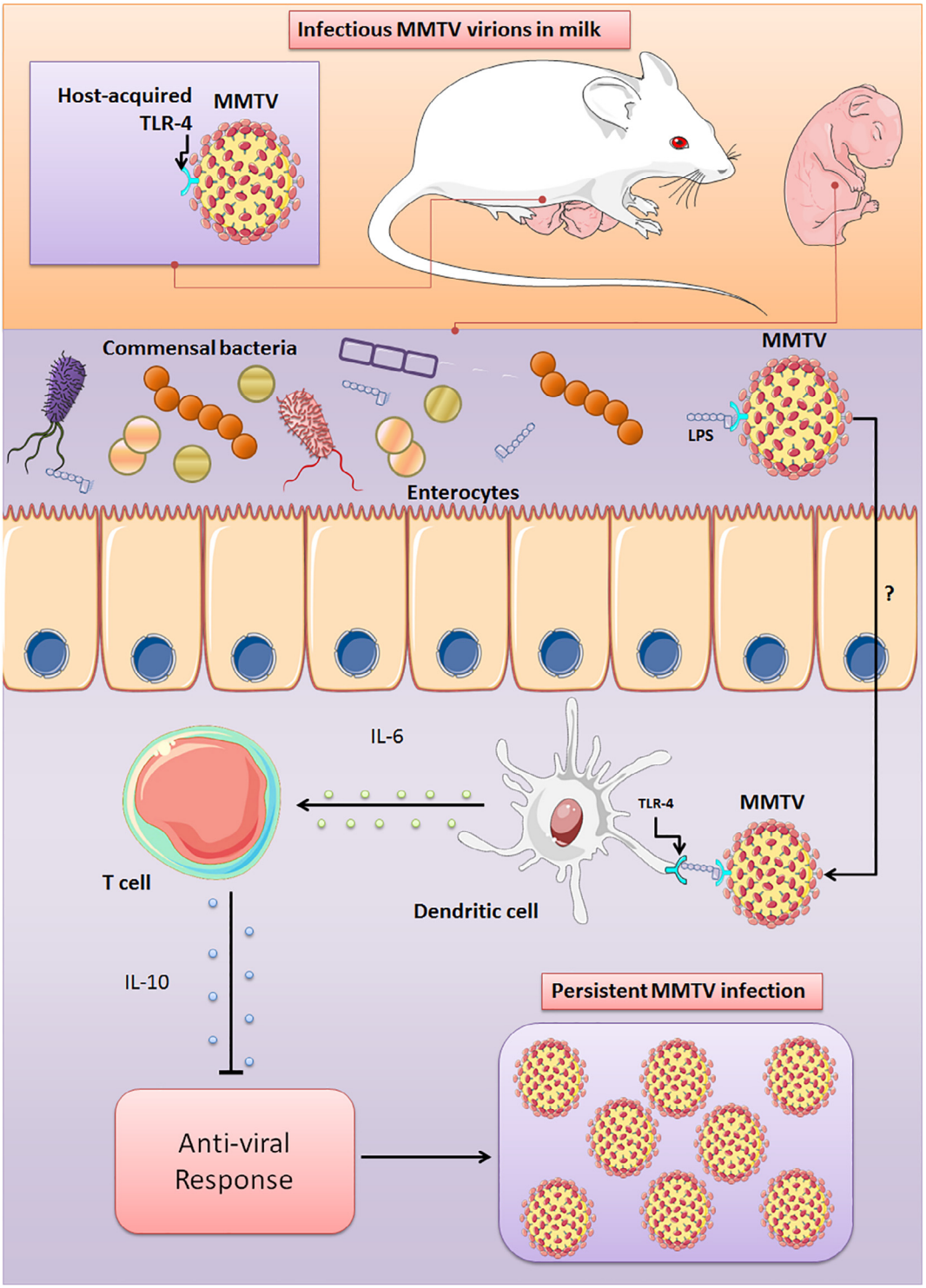

Fig. 2. Establishment of persistent MMTV infection in mice pups wherein regulatory T cells influence the antiviral immune response. The engagement of TLR4 (that was incorporated by MMTV) on LPS drives the production of IL-6, which induces IL-10 secretion. In this immunosuppressive microenvironment, MMTV is able to establish a persistent infection.

by *Lactobacillus* plays an important role as a natural antimicrobial agent in the vaginal ecosystem and is toxic to a numerous organisms, including viruses such as *Human immunodeficiency virus 1* (HIV-1) [43] and *Human alphaherpesvirus 2* (HSV-2) [44]. Another important *Lactobacillus* antimicrobial product is lactic acid, which is responsible for homeostasis of the female vaginal pH ($\leq$4.5)[45].This pH is the lowest in the vaginal ecosystem among all mammals and differs greatly from other primates ($\sim$pH 7.0) [45]. Lactobacilli generate L-lactic acid as a final product of the glycogen metabolism produced by mucosal epithelial cells. This acidic environment can inhibit the growth of several potentially pathogenic species, such as *Chlamydia trachomatis*, *Gardnerella vaginalis* in addition to inactivating HIV, HSV-2 and human papillomavirus type 16 (HPV-16), an *Alphapapillomavirus 9* [46–53] (Fig. 4A). The E5 protein of HPV-16, responsible for viral transformation, is known to be particularly susceptible to low pH [53]. In addition, vaginal microbiota dominated by *Lactobacillus gasseri* was associated

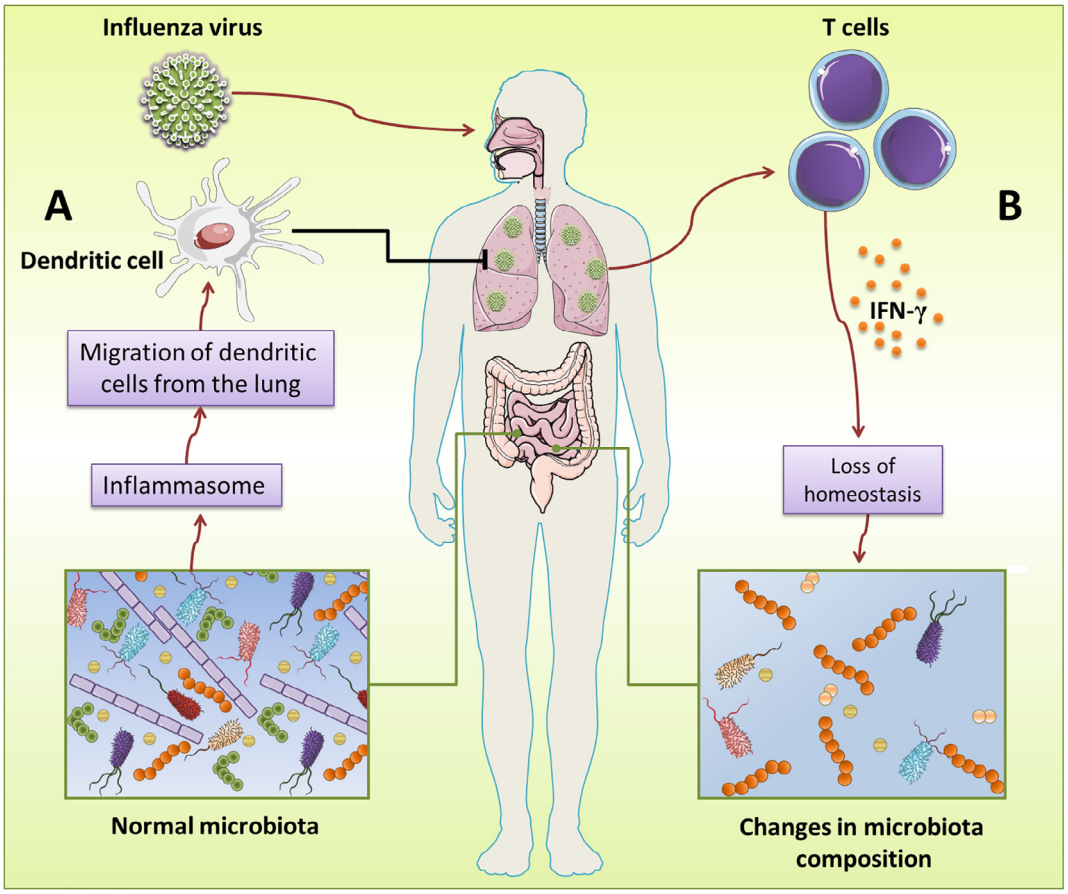

Fig. 3. Representative mechanism of the influence of the microbiota on influenza infection. (A) The migration of dendritic cells from the lung induced by inflammasome activation acts on influenza-specific T-cell responses characterizing a mechanism of microbiota-mediated protection against the influenza. (B) Influenza infection changes the intestinal microbiota composition mediated by IFN-γ produced by lung-derived T-cells recruited into the intestine.

with a faster clearance rate of detectable human papillomavirus (HPV) [54].

A comparative study of the primate vaginal microbiome showed that *Lactobacillus* dominance is an exclusive characteristic of humans and does not occur in non-human primates [45]. Importantly, women with bacterial vaginosis exhibit compositional similarities with non-human primates and a higher vaginal pH (pH = 5.5) than healthy women [55] (Fig. 4B). Bacterial vaginosis increases HSV-2 infection and has been linked to an increased risk of HIV-1 acquisition [56–58]. Vaginal microbiota may influence women's risk of HIV acquisition by some groups of microorganisms promotegenital inflammation and produce HIV-inducing factors in vaginal fluid, sialidases and mucinases that disrupt the protective cervicovaginal mucus layer [58–61]. Differences in the vaginal microbial diversity and concentrations of *Parvimonas* species types 1 and 2, *Gemella asaccharolytica*, *Mycoplasma hominis*, *Leptotrichia/Sneathia*, *Eggerthella* species type 1 and *Megasphaera* were significantly associated with increased risk of HIV acquisition in african women [58]. The majority of new HIV infections in Africa reached women women, unlike other parts of the world. Furthermore vaginal dysbiosis accounts for 20–30% of the population attributable risk of HIV acquisition in african women [58]. Additionally, in a study with Costa Rican pre-menopausal women, vaginal pH greater than 5.0 was shown to be significantly associated with a 10–20% increased risk of HPV positivity [62]. The characterization of the vaginal bacterial microbiota associated with HIV, HSV-2 and HPV risk provide important targets for future prevention research.

From an evolutionary perspective, humans and non-human primates differ considerably in mating habits, diet, estrus cycles, sexual behavior, gestation period and vaginal pH, these factors being associated with differences in microbial composition. To cross between animal species, a virus must overcome the barriers imposed by host biology and microbiota (Fig. 4C). An event related to this fact occurred recently for the HIV-1 origin through multiple events of cross-species transmission of *Simian immunodeficiency virus* (SIV) [63] (Fig. 4). In this case, it is essential to consider the aspects of the barriers imposed by the microbiota to better understand the path of the virus until it reaches its pandemic form and its epidemiology. This situation relates to the probability of women becoming infected with HIV-1 via vaginal intercourse, which is significantly lower than that of rectal or parenteral transmission [64].

5. Conclusion

In the last years, studies with poliovirus, norovirus, MMTV and influenza virus showed strict relationships between the microbiota and virus infections. These studies raised new questions and hypotheses that have remained largely unanswered, including the mechanism by which some viruses pass through the intestinal mucosa to reach their target cells. In view of the current findings about the affinity of viruses with the bacterial surface, the "microbial phoresy" traces a microbial parallel with the macroscopic animal world that could be an interesting model to explain how the viruses travel through the intestinal microbiota.

Another very interesting issue discussed here was the unusual features of the human healthy vaginal microbiota, such as the low pH and H_2O_2 presence. These features are effective barriers against various pathogens of the vaginal tract and a potential barrier against viral species cross transmission, such as for SIV-HIV where the probability of infection by this route is much lower than by others, but increased in

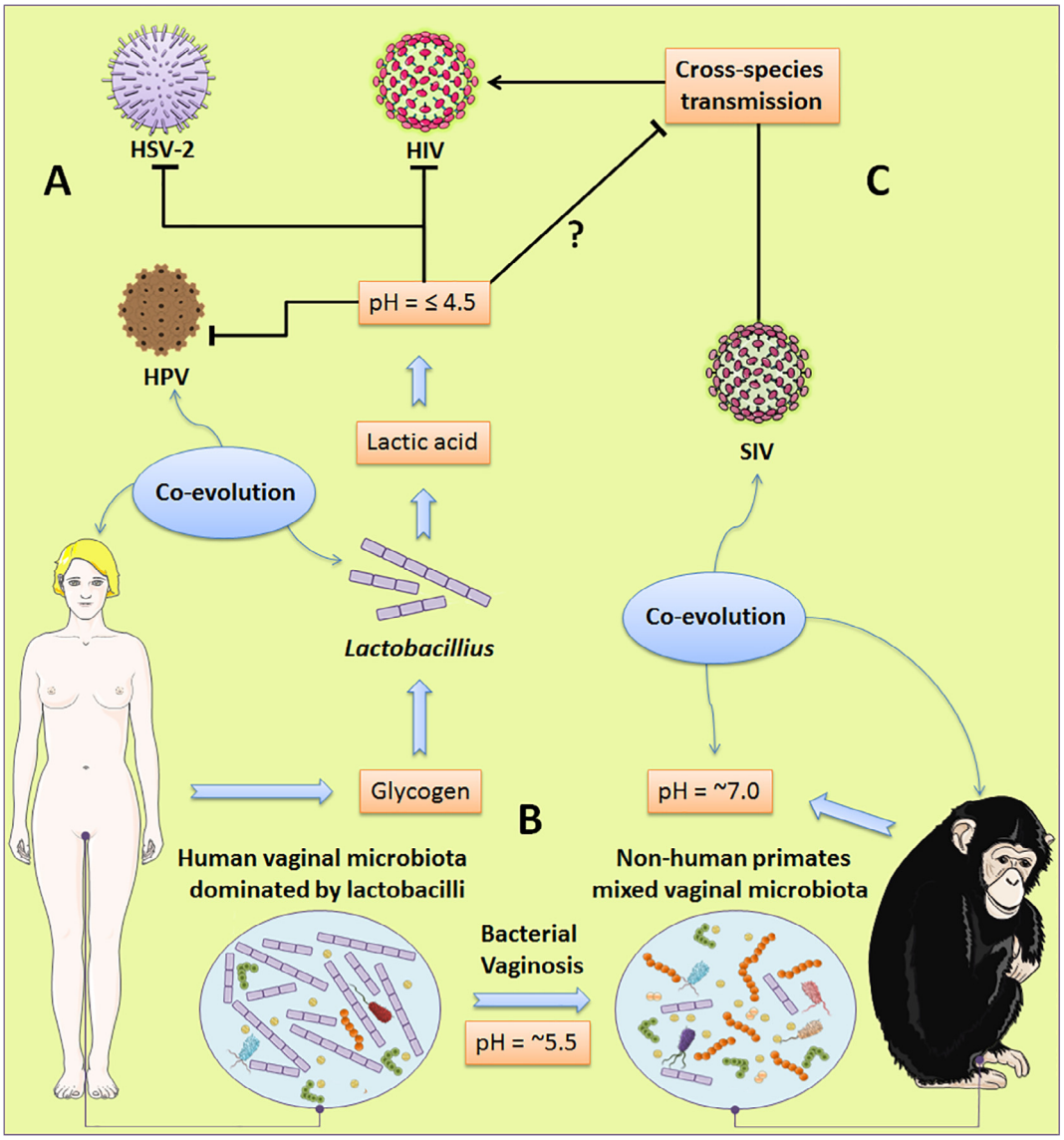

Fig. 4. The co-evolution of the human female vaginal microbiota with the *Lactobacillus* genus can inhibit several pathogenic species and create potential barriers to cross-species transmission. (A) An acidic environment can inhibit HIV, HSV-2 and HPV. (B) *Lactobacillus* dominance profile is exclusive to humans and does not occur in non-human primates. Women with bacterial vaginosis exhibit a higher vaginal pH than healthy women. (C) The origin of HIV-1 from cross-species transmission of *Simian immunodeficiency virus* (SIV). An acidic environment can create a potential barrier to cross-species transmission.

the situation of vaginal dysbiosis. An evolutionary hypothesis, named "disease risk hypothesis," proposes that humans face higher sexually transmitted disease risk than non-human mammals [65,66]. Humans show a more continuous sexual receptivity throughout the menstrual cycle, pregnancy, and the post-partum period [67]. This fact generates a selective pressure for the need of protective mechanisms, which could explain why *Lactobacillus* populations are higher in the human vaginal ecosystem compared to those of mammals with less frequent sexual contact [55].

We emphasize the need for further studies to better understand the regulatory relationships between the microbiota, the viral agents and the host immune system. The use of genomic and metagenomic tools is fundamental for the advancement of studies on microbiota-virus-host relationships given that little has been described about the amplitude of the virosphere. Taking as inspiration the famous phrase cited by the evolutionary biologist Theodosius Dobzhansky who says "Nothing in Biology Makes Sense Except in the Light of Evolution," we believe that an evolutionary perspective on microbiota-virus relationships is essential to discuss and unveil new aspects that remain in the dark.

Declaration of interest

We have no conflict of interest to declare.

Author contributions

Wrote the paper: MTL, ACSPA and GPO; designed the study, revised the content and final approved the final version: MTL, ACSPA, GPO, JRN, FSM, EGK and JSA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humic.2018.11.001.

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