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Interplay between viruses and bacterial microbiota in cancer development

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Abstract

During the last few decades we have become accustomed to the idea that viruses can cause tumors. It is much less considered and discussed, however, that most people infected with oncoviruses will never develop cancer. Therefore, the genetic and environmental factors that tip the scales from clearance of viral infection to development of cancer are currently an area of active investigation. Microbiota has recently emerged as a potentially critical factor that would affect this balance by increasing or decreasing the ability of viral infection to promote carcinogenesis. In this review, we provide a model of microbiome contribution to the development of oncogenic viral infections and viral associated cancers, give examples of this process in human tumors, and describe the challenges that prevent progress in the field as well as their potential solutions.

Keywords

Microbiota; Oncovirus; Microbiome; Virus-associated cancer; Transkingdom interactions

1. Introduction

As the human lifespan lengthens, the incidence of cancer worldwide is also increasing. The World Health Organization predicts the frequency of cancer occurrence to increase by 70% over the next two decades [1,2], indicating a rise in the global cancer epidemic. One of the established causes of cancer is viral infection, which is responsible for 20% of the global cancer burden [3]. Among these infections, the most common are Human Papilloma Virus (HPV) and Hepatitis C/B viruses with other less frequent contributors being Epstein - Barr virus (EBV), Human Immunodeficiency Virus (HIV), and Kaposi Sarcoma Herpesviruses (KSHV) [4]. These viruses use two different strategies to cause cancer: first, by directly affecting host cell machinery (e.g. HPV); and second, indirectly, by inhibiting the human immune system (e.g. HIV) [5,6]. It is common knowledge that the development of some cancers require viral infection, such as HPV for cervical cancer. It is less known, however, why most people infected with oncogenic viruses will never develop cancer.

A hint in solving this puzzle may come from studies demonstrating the crucial role of microbiota (collection of microorganisms living with the host) in the course of viral infections [7–10]. Moreover, microbiota have been recently implicated in different diseases associated with aberrant immune responses ranging from diabetes and autoimmunity to obesity and cancer [11,12]. For example, a recent epidemiologic study reported an association between antibiotic exposure and the development of several malignancies such as esophageal, gastric, pancreatic, lung, prostate, and breast cancers [13].

Studies thus far have placed emphasis on gastrointestinal microbiota and its role in the development and progression of gut-associated malignancies [14]. For example, *Helicobacter pylori* causes gastric adenocarcinoma and is a classic case of oncogenic bacteria [15]. Intestinal infections with other bacteria such as *Salmonella typhi* [16] and *Streptococcus gallolyticus* (*bovis*) [17] were also linked to the development of hepatobiliary and colorectal cancers, respectively. These studies represent additional support for the hypothesis that some microbiota members as an understudied environmental factor contributing to protection from or the development of virus-associated cancers. Even though the gut microbiome represents the majority of bacteria in the human microbiome [18], other body sites such as the vagina and oral cavity have been explored for their participation in cancer development and progression.

Although oncogenic properties of virus and bacteria, individually, are popular topics, the interaction between these in the context of cancer has not been well investigated. In recent years, we have witnessed an increasing number of attempts to interrogate this three-way interaction, particularly the influence of microbiota on the progression and acquisition of oncogenic viral infections. However, the question whether bacteria are beneficial or harmful in this context remains unanswered for many cancers. In this review, we provide a model of microbiome contribution to the development of oncogenic viral infections, discuss examples of this process in human tumors, and describe obstacles in the field and their potential solutions.

2. Model description

The role of bacteria (and bacterial microbiota) in viral infections leading to cancer can be assigned to two broad categories: bacteria that influence viral particles, and bacteria that affect host interaction with viral infection.

On the one hand, healthy microbiota was shown to contribute to infections by interacting with viruses directly and through bacterial byproducts [7–10]. It was reported that commensal microbiota augment the transmission of mouse mammary tumor virus [19,20], bacterial lipopolysaccharides enhance virion stability of poliovirus [21], and enteric bacteria promote norovirus infection through histo-blood group antigen-like substances [9,22]. On the other hand, healthy microbiota are critical for immune system development, especially on mucosal surfaces [23]. Antibiotic-treated mice exposed to mucosal influenza virus were observed to have impaired innate and adaptive antiviral immune responses and delayed clearance of the virus [24]. These and other studies define microbiota as a putatively important factor for the development of virus-associated cancers.

Herein we propose a model for the three-way interaction between bacteria, virus, and mammalian host, highlighting two distinct mechanisms for the contribution of microbiota to virus-associated cancers. The first involves the direct effect of interaction of bacteria and bacterial products on viruses, primarily affecting their infectivity (Fig. 1A). The second involves bacteria-host interactions leading to changes in host gene expression and subsequent activation/repression of viral expression or direct promotion of inflammation synergizing with the tumorigenic effects of a virus (Fig. 1B). There is evidence to suggest that the role of bacteria can be positive or negative in terms of disease progression with each of these cases. In this review, we discuss conventional tumor viruses and explore the role of gut, vaginal, and oral microbiota components in both of these mechanisms.

3. Gastrointestinal microbiome

The gut microbiome is the largest microbial community in the human body. Recent discoveries show its involvement in a variety of functions, including immune system training and metabolism regulation [25–27]. Separate members of gut microbiota as well as dysbiosis (i.e. non-specific alterations of mammalian microbial communities) have been implicated in disease development and progression. Among most prominent examples are diabetes [28], irritable bowel disease [25], and cancer [29,30]. Additionally, intestinal microbiota has been implicated in modulating the effect of different anti-cancer treatments [31–33]. Helicobacter species, in particular *Helicobacter pylori*, is the most well studied bacterial member of the gut community that causes cancer [15].

3.1. Hepatitis viruses

The second leading cause of cancer mortality is liver cancer [34]. The most prevalent histologic type of primary liver cancer is hepatocellular carcinoma (HCC) [35] primarily caused by chronic infection with hepatitis B (HBV) or hepatitis C (HCV) virus [36]. Although both viruses can cause cancer, HCV currently attracts stronger interest from the scientific community possibly due to the absence of a vaccine against HCV.

The pathogenicity of both HBV and HCV involves a combination of direct and indirect mechanisms. The HCV encoded core, nonstructural protein 5A (NS5A) and NS3, and HBV encoded X antigen (HBx) are able to promote host cell proliferation. Both viruses are similarly capable of blocking cell immune response, inhibiting apoptosis while promoting angiogenesis and metastasis. By contrast, chronic inflammation caused by oxidative stress also contributes to the process of carcinogenesis [6].

While HCV is oncogenic, not all patients suffering from chronic hepatitis C will develop cancer. One of the first indications that bacteria may be a critical parameter in liver cancer came with the observation that mice infected with Helicobacter were developing strong inflammatory responses leading to hepatocellular carcinoma [37]. Another group later found an association between *H. pylori* specific antibody levels and HCV associated hepatocellular carcinoma [38]. Helicobacter DNA was also found in liver and was associated with hepatitis C induced cirrhosis [39], which indicates the ability of *H. pylori* to invade the liver and putatively contribute to disease development (Fig. 2B). However, a more recent study conducted on HCV transgenic mice colonized with *H. pylori* found no indication of bacteria

translocation into the liver and no promotion of tumorigenesis [40]. Whether this experimental system failed to promote carcinogenesis, or *H. pylori* does not contribute to HCV-associated liver cancer, remains unknown.

Another *Helicobacter* species, *Helicobacter hepaticus*, has been shown to cause chronic hepatitis and liver cancer in rodents [37]. In the following study, Fox et al. have shown that presence of *H. hepaticus* in the gut lumen promotes development of hepatocellular carcinoma in HCV infected mice, acting synergistically with viral infection [41]. This process did not require bacterial invasion. Fox et al. also showed that in an aflatoxin B1 HCC mouse model, *H. hepaticus* induced the nuclear factor-κB (NF-κB) along with downstream innate and Th1-type adaptive immunity. In a HCV transgenic mouse model, they also observed increased gene expression of an NF-kB-dependent inflammatory chemokine (CXCL9) in mice colonized with *H. hepaticus* [6,41,42] (Fig. 2C, D). Concordantly in both models, tumor growth was accelerated in the presence of *H. hepaticus*. These bacteria, detected in human intestine [43] and liver [44–46], is suspected to contribute not only to cirrhosis [47] and HCC [44], but also to a set of other conditions such as inflammatory bowel disease [43] and prostate cancer [48]. Consequently, this data suggests a synergistic relationship between *H. hepaticus* and HCV in human cancers.

The link between HBV related oncogenesis and gut microbiota has also been reported. In 2011, Chen et al. found that enteric fungi diversity was positively correlated with a worsened disease state in chronic HBV infection [49]. More recently, Chou et al. showed that in adult C3H/HeN mice transfected with HBV, elimination of gut microbiota with antibiotics resulted in viral persistence phenotypes, including prolonged HBV surface antigens (HBsAg) presence, impaired anti-HBs production, and limited HBV core antigen (HBcAg)-specific IFN-γ–secreting splenocytes [50]. Although these results suggest that the persistence of HBV infection in antibiotic-treated mice is attributed to an ineffective adaptive humoral and cellular immune response, specific bacteria were not identified in this study. Other studies observed that a decrease in fecal *Bifidobacterium* populations was associated with liver disease progression of HBV infection in humans [51,52]. In addition, *Bifidobacterium* species have been shown to decrease the protein and transcript levels of HBsAg in a HBV-transfected human hepatoma cell line [53]. Interestingly, Bifidobacterium can also increase host gene expression of IFN-signaling components such as STAT1 [53] and lower serum cholesterol levels [54–56]. Furthermore, IFN stimulation have been shown to downregulate lipid metabolic pathways [27], known in host cells to be necessary for HBV production [57,58]. Therefore, we propose that *Bifidobacterium* species are able to stimulate IFN-dependent pathways which results in a downregulation of lipid metabolism and a reduction in HBV infection (Fig. 2A). Further experimentation is warranted to establish how the antiviral and antitumor effects of these bacteria contribute to overall protection against malignancy.

4. Cervicovaginal microbiome

Despite the fact that microbiota in the vagina is less diverse than in the gut it can also contribute to protection against or susceptibility to some illnesses, especially sexually transmitted diseases. Healthy stable vaginal microbiome is thought to be a first line of

defense [59,60] against diseases caused by opportunistic and true pathogens: outcompeting dangerous bacteria or protecting the host with bacterial by-products, in particular lactic acid [61–64] and hydrogen peroxide [60,65,66].

Lactobacilli, commonly considered as such beneficial microbes, represent the dominant genus [67,68] in healthy vaginal microbiota. However, this does not seem to be universally applicable as Gardnerella-dominated microbiomes were observed as another frequent type in some populations [69]. Disruption of healthy vaginal microbiota (bacterial vaginosis - BV) [67] may increase risks of sexually transmitted infections (STI) [70], and even contribute to the disease progression, putatively, including cancer development.

4.1. Human papillomavirus

Human papillomavirus (HPV) is the most common STI in the United States and although the majority of HPV types are non-carcinogenic, there are at least 13 high-risk oncogenic types (hrHPV), with HPV16 and HPV18 leading the list [71,72]. One of the most common cancers caused by HPV infection remains cervical squamous cell carcinoma. However, HPV is also linked to anal, vulvar, vaginal, penile and head-and-neck carcinomas [73].

hrHPV infections remain the main predictors for cervical intraepithelial neoplasia (CIN), precursor to tumor, and cervical cancer development itself [74–76]. HPV infects basal epithelial cells. After infection HPV either exist in episomal form or can integrate into the cell genome causing genomic instability. Expression of HPV oncogenes E6 and E7 is also dependent on integration: in episomal form expression of E2 protein keeps expression levels of E6/7 low, but during integration open reading frame of E2 gene is disrupted and E2 no longer is able to control HPV oncogenes. E6, E7 and E5 HPV oncoproteins retain keratinocytes in proliferative state, avoiding apoptosis and clearance by the immune system. It was also reported that HPV is able to promote angiogenesis and deregulate cellular energetics [77].

Although hrHPV type infections are necessary for development of cervical cancer, in most cases the virus is cleared by the host. Only 0.3–1.2% of women eventually develop cervical cancer [78] which means that additional risk factors contribute to the disease progression and vaginal microbiota is possibly one of them. It appears that both, the protective role of normal vaginal microbiome and the contribution of certain pathogens, may play a role in development of cervical intraepithelial lesions and cancer.

While *Lactobacillus gasseri*-dominated vaginal bacterial communities are associated with faster clearance of HPV infection [79], dysbiosis, and bacterial vaginosis are associated with CIN development and progression [80,81] (Fig. 3D). Furthermore, it is unclear whether bacteria in the disrupted vaginal microbiome affect host susceptibility, virus survival, or infectivity. Some evidence (discussed below), however, points to the possible involvement of Prevotella genus that contains *Prevotella bivia*, a microbe known to be associated with bacterial vaginosis.

Normally inhibited by Lactobacillus [65], Prevotella species may become abundant when the homeostasis of the vaginal microbial community is disrupted by such factors as diet or

hormone status [82] (Fig. 3E). Recent findings also suggest host genetics as an important factor in Prevotella outgrowth [82]. Increasing in abundance, Prevotella species may provide nutrients (e.g. ammonia and amino acids), to other members of microbial community such as *Gardnerella vaginalis* and *Peptostreptococcus anaerobius* [83,84], and thus diversify the vaginal microbial landscape [69] (Fig. 3F). Furthermore, multiple studies of Prevotella associations with bacterial vaginosis and cervicitis [68,82,85] point to Prevotella as a conductor orchestrating the state of vaginal microbiomes. Additionally, a clear link between Prevotella genus and HPV infection [86], in particular with high risk HPV types [87], has been established. Adding to the potential importance of these microbes, Prevotella was cultured from cervical cancer samples in 1993 [88], and more recently we detected it as the most abundant genus in cervical cancer biopsies (unpublished). Finally, increased expression of NF-κB, Toll-like receptor (TLR), NOD-like receptor, and TNF-α signaling pathways in antigen presenting cells from blood, and increased levels of pro-inflammatory cytokines from vaginal lavage have been associated with microbial communities that include Prevotella [69]. Thus, it is likely that Prevotella or Prevotella-driven vaginal microbiome may act in favor of persistent HPV infection promoting cervical cancer development through upregulation of cell proliferation and chronic inflammation.

Aside from the common members of vaginal microbiota, pathogens have also been suspected in the promotion of HPV infection. For example, *Chlamydia trachomatis*, has been studied for some time as a potential co-factor of HPV in the process of tumorigenesis [89,90]. Investigation of the potential mechanism of how *C. trachomatis* infection may influence HPV infection and cancer development are underway. For example, it was demonstrated that *C. trachomatis* can decrease the expression of caveolin-1 (tumor suppressor) and increase C-myc mRNA levels (oncogene) [91]. A study conducted by Paba et al. found a correlation between *C. trichomonas* infection and upregulation of cytoplasmic and nuclear NF-kB, VEGF-c and survivin in HPV-positive CINs and cervical cancer [92], which points out to the possibility that *C. trachomatis* can also act through the NF-kB pathway, promoting local inflammation, cell survival and proliferation (Fig. 3G). Despite many studies and even mechanistic research, the scientific community has not yet reached a consensus about whether *C. trachomatis* plays a causal role in aiding HPV in carcinogenesis. Thus epidemiological studies that would investigate the temporal relationship between *C. trachomatis* and HPV infections are required to settle this long standing debate.

4.2. Human immunodeficiency virus

Human Immunodeficiency Virus (HIV) is a carcinogenic virus in its ability to act as a co-factor for EBV and KSHV in carcinogenesis [93]. Immunosuppression, chronic antigenic stimulation, and cytokine dysregulation are reported to contribute to HIV-associated cancer development. However, the main cause of HIV-related cancer development remains immunosuppression: the inability of the immune system to recognize and clear host cells infected with potentially oncogenic viruses enables those viruses to express oncogenic proteins, which in its turn leads to cancer development [6]. Due to the absence of vaccines and ways to eliminate HIV, understanding risk factors contributing to the pathogenesis of HIV infections becomes a priority.

Sexual transmission is one of the most common ways to acquire HIV, suggesting that vaginal microbiota may influence this process. Indeed, several studies found an association between the risk of HIV infection and bacterial vaginosis [94–96]. However, it is still unclear whether the absence or overgrowth of some bacteria in the vaginal microbiota would make women more susceptible to or protected from HIV infection.

In 2013, Aldunate et al. showed that physiological concentrations of lactic acid can inactivate different HIV subtypes [97]. Thus, *Lactobacillus* spp. which is known to produce lactic acid, may play an important role in protection against sexually transmitted diseases, including HIV [98] (Fig. 3A). In contrast, bacterial vaginosis predisposes females to sexually transmitted diseases [99], and can reactivate latent HIV infection [100,101]. Evidence suggests that bacteria are not acting directly on HIV, but rather via bacterial by-products (e.g. butyric acid) [105,106]. Specifically, immunosuppression caused by HIV is an important step in the establishment of lifelong latent infection and avoidance of host immune response. Latently infected cells harbor the HIV proviral DNA genome integrated into heterochromatin, allowing the persistence of transcriptionally silent proviruses [102]. Hypoacetylation of histone proteins by histone deacetylases (HDAC) is involved in the maintenance of HIV latency by repressing viral transcription [103,104]. Interestingly, butyric acid-producing bacteria (*Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Clostridium cochlearium*, *Eubacterium multiforme*, and *Anaerococcus tetradius*), residing in different mucosal environments (gut, vaginal, and oral cavities), are capable of reactivating latent HIV infection through host HDAC pathways [105,106] (Figs. 3B, 4B). Butyric acid is known to inhibit the enzymatic activity of HDAC by directly competing with HDAC substrate at the catalytic center of the enzyme [107] (Fig. 4A). Butyrate originating from microbiota has been shown to promote immunosuppressive/immunoregulatory effects [108]. Considering this, it is plausible that in addition to reactivating viruses, butyric acid can inhibit antiviral immunity in the host directly.

Additionally, the epidemiological synergy of sexually transmitted infections (STI) with HIV transmission was reported in multiple studies. Ferreira et al. found that stimulation of HIV infected T-cells with TLR3, 4, or 5 ligands leads to enhanced HIV-1 replication via direct activation of HIV long terminal repeats, or by inducing secreted factors that promote HIV replication [109]. Among the pathogens suspected to contribute to HIV infection and reactivation, one player stands out - *Neisseria gonorrhoeae*: it was found to be highly associated with HIV infection [110] and activation of HIV expression [109,111,112]. Not only does *N. gonorrhoeae* drives an increase of activated CD4+ T-cells [111] and pro-inflammatory cytokines in genital epithelial cells such as IL-6, IL-8 and TNFα [109], but exposure to the pathogen directly drives HIV expression in T cells in NF-kB and AP-1 dependent manner [109,111]. Malott et al. showed that *N. gonorrhoeae* by-product heptose-monophosphate is necessary for invoking these host responses [111] (Fig. 3C). Thus, the course of HIV infection can be altered negatively (by lactate producers) or positively (by butyrate producers or *N. gonorrhoeae*), preventing or favoring, respectively, development of immunodeficiency, which may increase susceptibility to EBV and KSHV infection, which are responsible for a substantial proportion of HIV-related cancers.

5. Oral microbiome

Although many studies have been devoted to HIV in the genital tract, the connection between HIV, oral microbiome, and periodontal disease has also drawn the attention of the scientific community [113–116] [105,106]. Recent works have found associations between periodontitis, a chronic inflammatory disease of the periodontium occurring in response to bacterial infection, and several types of oral cancers [117–120]. Periodontal disease is marked by a disruption in the oral microbiome and is often associated with a shift to anaerobic bacteria such as *Porphyromonas gingivalis*, that has also been directly implicated in cancers [121,122]. Although common risk factors for these cancers include smoking and alcohol abuse, there are an increasing number of cases where no significant smoking or drinking history has been reported. Among other risk factors are viral infections HIV, HPV, herpesviruses (EBV, HCMV, KSHV) and oral hygiene [123]. Herpes-viruses, particularly EBV and KSHV, are known to cause cancer in the context of immunodeficiency caused by HIV/AIDS [124].

5.1. Herpesviruses

Herpesviruses have recently been implicated in the progression of periodontitis in the oral cavity [125–129]. Among these viruses, KSHV, EBV, and HCMV have also been associated with head and neck cancers, primarily those found in the mouth. A hallmark of herpesviruses is their ability to establish life-long latent infection in host cells. During latent infection, certain viral genes are repressed and viral progenies are not produced. The reactivation of lytic cycle genes in virus-infected cells marks the production of viral progeny which ultimately leads to host cell lysis. Both latent and lytic cycle genes are critical for tumorigenesis and the evasion of host immune response. In addition, studies exploring co-infection and crosstalk between these viruses as well as with HIV has shown direct (virus-virus) and indirect (through host immunity) interactions, most notably affecting the transition between latent and lytic viral cycles [124,130].

Human cytomegalovirus (HCMV) is not usually regarded as an oncogenic virus. However, HCMV infections have been implicated in malignant diseases from different cancer entities and can cause fatal diseases in immunocompromised patients [131]. Some evidence also suggests its role in sustaining chronic inflammation in the progression of cancer [132]. However, in the case of oral squamous cell carcinomas, Saravani et al. reported that only 6.3% of 48 patient samples were found to have detectable HCMV [133]. Although this patient population had low incidence of HCMV detection, it does not discount the possibility of synergy between HCMV and periodontal disease (not explored) in the development of oral cancer subtypes. In fact, HCMV has been associated with active periodontal disease and *P. gingivalis* [126–129]. Thus, strengthening the argument to keep HCMV among potential co-factors contributing to chronic inflammation that leads to oral tumorigenesis.

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is a herpesvirus that has become a well-known oncovirus in immunocompromised individuals infected with HIV [134]. This virus is consistently associated with Kaposi's sarcoma, a cancer developed from cells that line the lymph or blood vessels and usually appears as a tumor on the skin or mucosal [135]. Latent transcripts in KSHV include genes

and miRNAs that favor viral persistence and replication while promoting host-cell proliferation and survival. Furthermore, lytic cycle genes favor viral replication by affecting the DNA damage response, reprogramming metabolism, promoting survival, and mediating immune evasion, all of which have a role in promoting cancer development [6]. In 2007, Morris et al. explored the effects of supernatants from cultures of different bacteria on KSHV infected BCLBL-1 cells [136]. They found that metabolic end products from pathogens (gram-negative anaerobic periodontopathogens *F. nucleatum* and *P. gingivalis*) induced lytic replication of KSHV through the activation of a stress-activated MAPK pathway in host cells. More specifically, butyric acid from bacteria supernatants were found to inhibit cellular HDACs and activate the p38 kinases pathway, resulting in hyperacetylation of histones on immediate early viral promoters (Fig. 4C). The targeting of HDACs by *P. gingivalis* is also seen in the reactivation of HIV as we discussed previously.

Epstein–Barr virus (EBV) was the first virus shown to cause cancer in humans and is associated with a wide range of human cancers originating from epithelial cells, lymphocytes and mesenchymal cells [137]. Infection is transmitted from host to host via salivary contact, and the virus passes through the oropharyngeal epithelium to B lymphocytes, where it establishes a lifelong latent infection. EBV has three main latency patterns, each of which have a role in avoiding host response while promoting B-cell survival/proliferation [6]. Although not deeply studied, there is increasing evidence that EBV early lytic genes, particularly those encoding homologues of Bcl-2 (BALF1), IL-10 (BCRF1) and c-fms receptor (BARF1), may be involved in oncogenesis as well as in promoting viral infection. Reactivation of the virus and production of progeny contributes to several human diseases including nasopharyngeal carcinomas and lymphomas [138]. Similar to KSHV and HIV, the latent virus was found to be reactivated upon stimulation with supernatant from *P. gingivalis* (containing high concentrations of butyric acid) through the inhibition of HDACs [138]. This inhibition resulted in increased acetylation of adjacent histone and transcriptional activation of the BZLF1 promoter, whose gene product ZEBRA is known to be the master regulator in EBV transition from latency to lytic state [138] (Fig. 4D). Taken together with the case of KSHV, there is compelling evidence for the ability of butyric acid producing bacteria such as *P. gingivalis* (main player in periodontitis) to reactivate latent herpesvirus infection and contribute to the development of cancer in the oral cavity.

As described above, butyric-acid producing bacteria (especially the periodontopathogens *P. gingivalis*) can regulate the viral life cycle in host cells. Periodontopathogens can induce a reactivation of HIV which in turn may lead to the opportunistic infection of herpesviruses due to immunodeficiency. Latent infection of EBV and KSHV can be reactivated by the same bacteria leading to the induction of oncogenes and transformation to malignancy. Independent of bacteria, a model of KSHV and EBV co-infection *in vitro* has shown complementing lytic activation [139], suggesting a more complex model of reactivation in which periodontopathogens may act in tandem with direct inter-viral interaction to regulate infection and the development of cancers. Although HCMV has not been studied extensively in the same context, its association with *P. gingivalis* and periodontal disease offers hints of viral-bacterial interaction potentially involving mechanisms used by other herpesviruses.

6. Human endogenous retroviruses

Endogenous retroviruses (ERVs) are endogenous viral elements located in the genome of jawed vertebrates, including humans, and are thought to be relics of ancestral infectious retroviruses [140]. Human endogenous retroviruses (HERVs) compose about 4–8% of human genome [141]. While there is not enough evidence to solidify the role of HERVs in causing human cancers, the connection between the two is constantly been researched [140]. Reactivation of HERV expression in cancers [140,142] can contribute to genome instability and is suspected to be a prominent player in disease development. Furthermore, resurrection of murine leukemia virus (MLV) in immunocompromised mice was found to be dependent on intestinal microbiota [143]. In humans, environmental and intestinal microbes were able to modulate the transcriptional activity of endogenous retroviruses [144]. It is not clear whether this process contributes to cancer development. Nonetheless, multiple studies show that upregulated HERV expression in cancerous cells can drive inflammatory responses by upregulating type I interferon pathways [145–147] and eliciting T-cell specific antitumor immunity [148]. These findings may indicate the role of the immune system in recognizing the reactivation of "sleeping" HERVs as a sign of cell transformation and clearing the potential threat before it develops into malignancies.

7. Risk factors of virus-associated cancers and microbiome

Risk factors for cancer, such as age, lifestyle, diet and genetics, have been identified but the mechanisms underlying their contribution to disease are not always well understood [149,150]. The discovery of the role of commensal microbiota and pathobionts in cancer development and progression suggests that at least some risk factors may be linked to the disease through microbiota. For example, while smoking is a risk factor for nasopharyngeal carcinoma [151], it is also associated with dysbiosis in oral microbiota [152], which in its turn can contribute to periodontal disease leading to cancer development [153]. In cervical cancer, a high number of sexual partners is a well-known risk factor. This association has been commonly attributed to increased chances to be exposed to high risk HPV [154]. However, women with multiple sexual partners also present disruption of vaginal microbiota (bacterial vaginosis) [155,156] that may facilitate chronic HPV infection and cervical cancer as discussed earlier (Section 4.1). Another example is liver cancer, for which diabetes and obesity have been identified as risk factors [149,157]. Interestingly, in obese people among many changes in the gut microbiome, a decrease in *Bifidobacterium* was reported [158]. Because this bacterium has been shown to play a positive role in elimination of HBV (as described in Section 3.1), this may partially explain the association between diet-induced obesity and liver cancer. Although environmental and hereditary factors make virus-bacteria-host interactions even more complex to investigate, it is crucial to remember that understanding the role of these external factors may become a powerful tool for cancer prevention and treatment.

8. Summary

It has recently become evident that progress in the field of virus-associated cancers can be enhanced by elucidation of how bacterial microbiota contributes to virus-host interaction.

Although the dissection of these transkingdom interactions is evolving [159], we are still in the early stages of this journey. Indeed, epidemiological and even some mechanistic studies are accumulating. However, the scientific community has not yet reached a unanimous agreement on whether any specific cancer requires bacteria-virus interaction for carcinogenesis.

Herein, we have described a model of bacteria-virus interactions in the development of cancer. We identify two main mechanisms; the first is accomplished by the interaction between bacteria and virus resulting in changes in the course of viral infection. The most notable example of such mechanism is the inactivation of HIV via bacteria-derived lactic acid [97]. The second mechanism is an effect of the bacteria on the host resulting in alterations of host susceptibility to viral infection. This can happen in several ways: a) bacteria inducing pro-tumor chronic inflammation (e.g. activation of NF-kB pathway [6,41,69,92,109,111]), b) commensal bacteria promoting antiviral and antitumor immunity (e.g. Bifidobacterium in HBV [53,160]), and c) bacterial metabolite reactivating oncoviruses (butyric acid inhibition of host HDAC pathways reactivating HIV [105,106], EBV [138], KSHV [136]) (Table 1).

In addition to proposing the model, we identified key questions that have to be answered in order to move the field forward (Box 1) and major technological/logistical solutions that are required to answer these questions (Box 2).

Finally, treatment of cancer with chemicals and radiation are currently the most popular and efficient strategies [161,162]. More recently, our armamentarium was advanced with vaccines against oncoviruses [163] and immunotherapy [164], both using the immune system to prevent or kill cancer. Unfortunately, neither of these strategies allowed us to eliminate completely any oncovirus, nor to cure some cancers.

Therefore, novel approaches are required to significantly change the status quo of this field. We believe that this change should come with methods promoting a healthy microbiome, development of next generation antibiotics targeting individual bacteria, new probiotics, and companion diagnostics that will define a course of personalized/precision medicine for each individual patient based on their respective transcriptome and microbiome.

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Box 1

Current trending questions

- Which shifts in microbial communities (presence/absence of particular bacterial species or alterations in microbial community structures) can enhance oncogenic virus infection progression or, on the contrary, help to eliminate it?

- Which host molecular pathways involved in viral infections and tumorigenesis are altered by microbiota?

- Can host genetics shape microbiota toward being anti- or pro-tumorigenic?

- How do microbiota affect the success of anticancer therapies?

- How do antitumor treatments affect microbiota? Are these effects relevant for efficient treatments and treatment-related co-morbidities?

Box 2

## Emerging technologies and other solutions

- Experimental approaches for the generation of different types of omics data that would allow simultaneous assessment of functional states of each of viruses, host and bacteria (e.g. new and improved single cell technologies for both eukaryotic and prokaryotic cells).

- Computational tools for the analysis of multi-omics datasets that would provide robust predictions of regulatory relationships between all three kingdoms (e.g. transkingdom networks [165,166], LEfSe [167]).

- Generation of new experimental models: a) humanized animal models (e.g. gnotobiotic animal models for cancer caused by oncogenic viruses harboring human microbiota and immune system); b) cell lines and tissues with virus and bacteria present (e.g. differentiated 3D cell aggregates colonized with specific bacteria [168–173]); c) next generation in vitro models such as organ-on-chip and human-on-chip microfluidic devices that allow application of robotic systems.

- Creation of multidisciplinary teams (involving oncologists with expertise in basic and clinical science, systems biologist, virologist, microbiologists, and engineers) through special funding mechanisms or even the creation of new institutions.
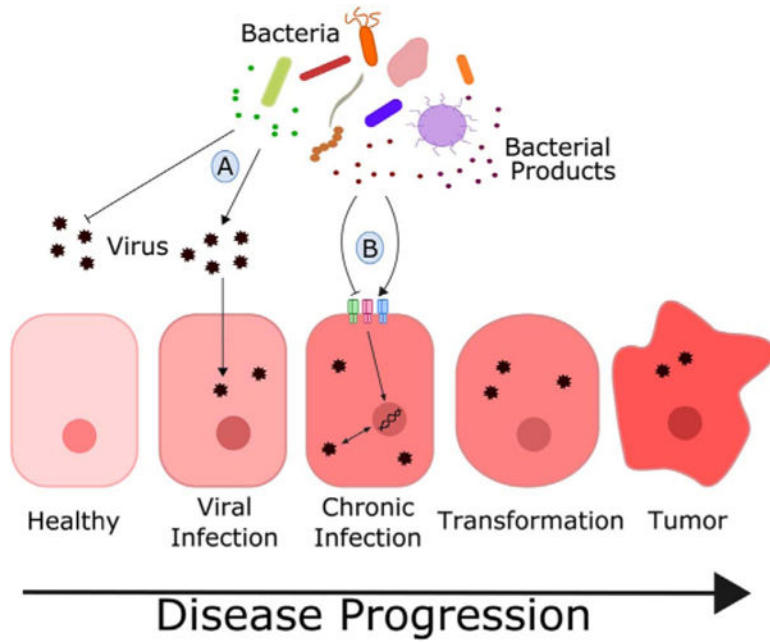
Fig. 1.
Model of bacteria-virus interactions in cancer development and progression: A) direct interaction between bacteria or bacterial by-products and virus resulting in inhibition or promotion of viral infection into host cell; B) indirect interaction between bacteria and virus mediated by host response to bacterial stimuli through activation of various pattern recognition receptors.
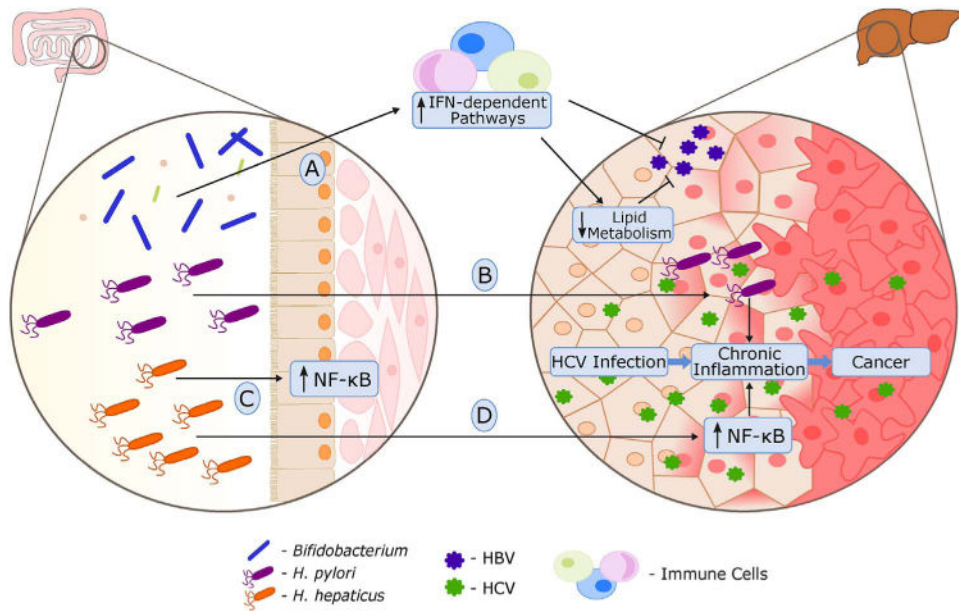
Fig. 2.
The interplay between gut microbiome, host and human hepatitis viruses (HCV and HBV):
A) healthy gut microbiota stimulates host immune system resulting in HBV infection
clearance; B) *Helicobacter pylori* invades liver and contributes to chronic inflammation
induced by HCV; C, D) *Helicobacter hepaticus* upregulates NF-κB dependent pathways in
mouse gut (C) and liver (D), synergizing with HCV-related inflammation in the development
of hepatocellular carcinoma.
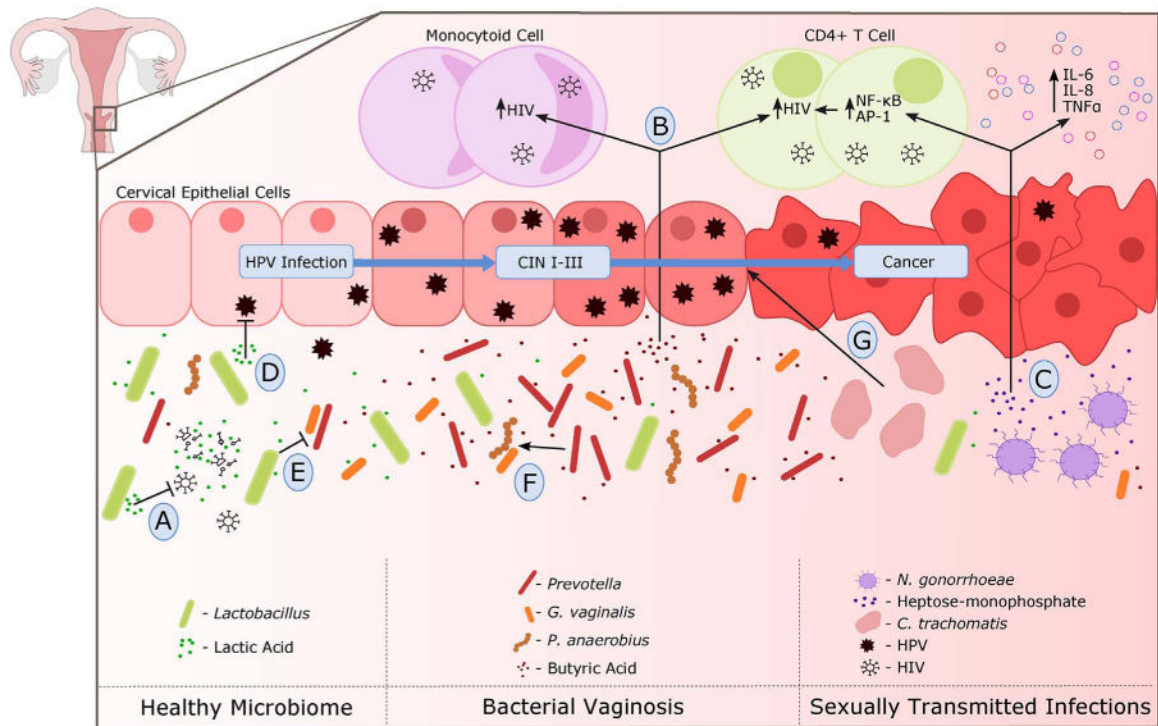
Fig. 3.

Cervicovaginal microbiota and pathogens can influence the progression of viral infection associated with cancer development: A) *Lactobacillus* spp., predominant bacteria in the vaginal microbiome, secretes lactic acid capable of inactivating HIV; B) butyric acid secreted by vaginal microbiota induces HIV replication in Human CD4+ T lymphocyte and macrophage/monocyte cell lines harboring latent HIV; C) *Neisseria gonorrhoeae* induces IL-6, IL-8 and TNFα production in genital epithelial cells and upregulates HIV gene expression in T-cells via heptose-monophosphate induced NF-kB and AP-1 pathways; D) domination of vaginal microbiota by *Lactobacillus gasseri* is associated with faster HPV clearance; E) *Lactobacillus* spp. is able to inhibit the viability of *Gardnerella vaginalis* and *Prevotella bivia*; F) *Prevotella* spp. produces ammonia and different amino acids that benefit *G. vaginalis* and *Peptostreptococcus anaerobius*, contributing to bacterial vaginosis; G) *Chlamydia trichomatis* may influence cervical cancer development, either through synergy with HPV or by contributing to local chronic inflammation.
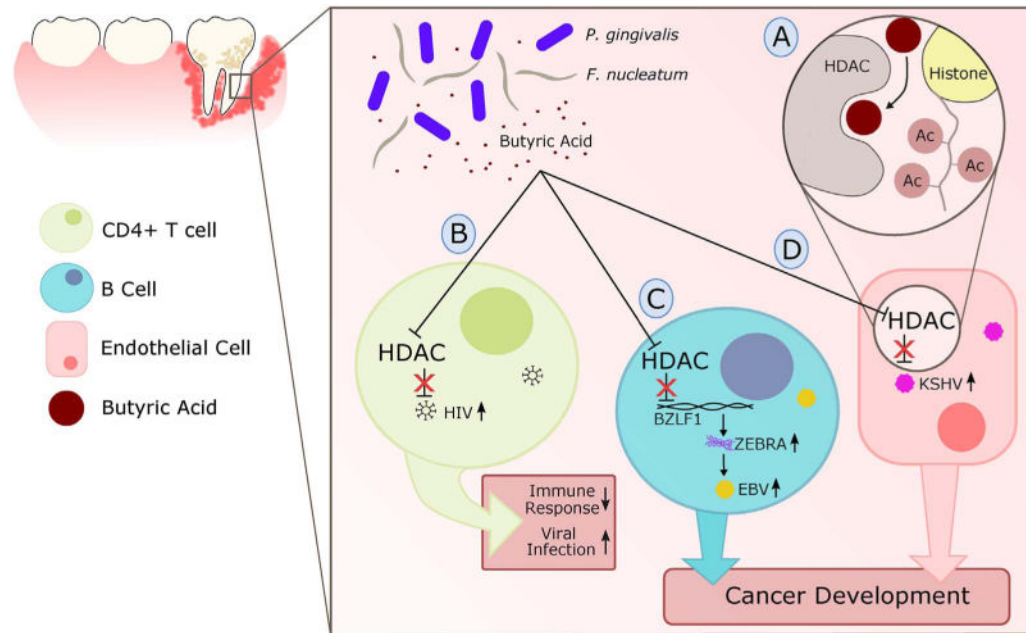
Fig. 4.
The role of periodontal disease in head and neck cancers can be mediated by the effects of HIV and herpesviruses (EBV and KSHV): A) butyric acid produced by periodontal pathogens such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis* competitively inhibit Histone Deacetylases (HDACs), resulting in the reduced deacetylation of histone proteins and sustaining viral gene expression B) activation of HIV proviral gene expression through HDAC inhibition increases viral progeny production; HIV infection suppresses systemic immune responses and aides in the acquisition of other viral infections; C) inhibition of HDAC causes transcriptional activation of the BZLF1 promoter in EBV infected cells and results in production of ZEBRA, known switch for lytic cycle activation; D) inhibition of HDACs in KSHV-associated cells result in the induction of MAPK and expression of lytic genes. Both EBV (C) and KSHV (D) mechanisms promote the spread of viral infection and contributes to tumor development.

Table 1

Summary of findings for each virus discussed in this review. Information presented is limited to the scope of the article.

Virus	Viral Location	Cancer Type	Bacteria-Virus Interaction	Microbiome Location	Bacteria	Bacterial By-products	Bacteria Impact on Host
HCV	liver	hepatocellular carcinoma	indirect	gut, liver	*Helicobacter pylori* [37–39], *Helicobacter hepaticus* [37,41]		activation of NF-κB [6,41] cirrhosis [47] HCC [44]
HBV	liver	hepatocellular carcinoma	indirect	gut	Bifidobacterium [51,52]		HBV clearance [50,53] anti-tumor immunity [160] up-regulation of IFN-dependent pathways [53] lower serum cholesterol [54–56]
HPV	vaginal	cervical	indirect	vaginal	*Lactobacillus gasseri* [79] BV-associated [80,81] *Chlamydia trachomatis* [74–76,89,174,175] *Prevotella* [86,87]		decrease caveolin-1 and increase C-myc [91] upregulation of NF-kB, VEGF-c and survivin [92] upregulation of NF-κB, Toll-like receptor (TLR), NOD-like receptor, and TNF-α signaling pathways [69]
HIV	lymphoid cells	head & neck, cervical, Kaposi's sarcoma	direct, indirect	gut, oral, vaginal	BV-associated [100,101] *Neisseria gonorrhoeae* [109–112] butyric acid producing bacteria [105,106]	lactic acid [97] heptose-monophosphate [111] butyric acid [105,106]	TLR3,4,5 [109] activated CD4+ T-cells [111] pro-inflammatory cytokines [109] NF-kB and AP-1 [109,111] inhibit HDAC [105,106]
HCMV	oral	head & neck		oral	*Porphyromonas gingivalis* [126–129]		

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Virus	Viral Location	Cancer Type	Bacteria-Virus Interaction	Microbiome Location	Bacteria	Bacterial By-products	Bacteria Impact on Host
KSHV	oral	Kaposi's sarcoma	indirect	oral	*Porphyromonas gingivalis* [125–128,136] *Fusobacterium nucleatum* [136]	butyric acid [136]	inhibit HDAC and activate p38 [136]
EBV	B lymphocytes	nasopharyngeal carcinoma	indirect (host)	oral	*Porphyromonas gingivalis* [138]	butyric acid [138]	inhibit HDAC and activate BZLF1 promoter [138]
HERVs			indirect	gut			upregulation of type I interferon pathways [145–147] T-cells specific antitumor immunity [148]