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Current Opinion in Virology

Virome and bacteriome: two sides of the same coin

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Although bacterial dysbiosis has been previously associated with carcinogenesis and HIV infection, the impact of the virome and these disease states has been less well studied. In this review, we will summarize what is known about the interplay between both the bacterial and the viral components of the microbiome on cancer and HIV pathogenesis. Bacterial dysbiosis has been associated with carcinogenesis such as colorectal cancer (CRC), hepatocellular carcinoma (HCC), lung cancer, breast cancer, and gastric cancer. The dysbiotic pathogenesis may be species-based or community-based and can have varying mechanisms of carcinogenesis. The human virome was also associated with certain cancers. Viruses, such as cytomegalovirus (CMV), Human herpesvirus 8 (HHV-8), human papilloma virus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and Epstein–Barr virus (EBV), all had associations with cancers. It was also reported that an altered bacteriophage community may lead to carcinogenesis by allowing opportunistic, oncogenic bacteria to proliferate in a gastrointestinal biofilm. This mechanism shows the importance of analyzing the bacteriome and the virome concurrently as their interactions can provide insight into new mechanisms in the pathogenesis of not only cancer, but other diseases as well. The enteric bacteriome was shown to be distinctly altered in immunocompromised HIV-infected individuals, and highly active antiretroviral therapy (HAART) was shown to at least partially reverse the alterations that HIV causes in the bacteriome. Studies have shown that the progression to HIV is associated with changes in the plasma concentration of commensal viruses. HIV also acts synergistically with multiple other viruses, such as HPV, EBV, varicella zoster virus (VZV), and HHV-8. Although it has been shown that HIV infection leads to enteric virome expansion in humans, most of the research on HIV's effect on the virome was conducted in non-human primates, and there is a lack of research on the effect of HAART on the virome. Virome-wide analysis is necessary for identifying novel viral etiologies. There is currently a wealth of information on the bacteriome and its associations with cancer and HIV, but more research should be conducted on the virome's associations and reaction to HAART as well as the bacteriome-virome interactions that may play a major role in pathogenesis and recovery.

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Introduction

It has long been known that the human body contains an abundance of microorganisms, such as bacteria, viruses, archaea, and fungi that reside in the gastrointestinal tract (GIT), lungs, skin, and other organs, known collectively as the microbiome. The bacterial microbiome, or bacteriome, changes throughout life due to environmental factors as well as host genetic factors and has a wide range of effects on human health. Prebiotics or probiotics, which are used to restore the microbiome back to health, have been used to treat constipation, allergies, and inflammatory bowel syndrome (IBS) and fecal transplants have been effective in treating *Clostridium difficile* infections [1]. The virome is the most diverse and abundant collection of parasites in the human body and primarily consists of animal-infecting viruses, which may be transient or chronic, and bacteriophages, which infect bacteria and may be lytic or lysogenic. The associations between the human bacteriome and major diseases, such as cancer and HIV, have been extensively researched; however, the virome has not been analyzed as extensively. In this review, we look at the effects that the bacteriome and virome may have on the progression and recovery of cancer and HIV.

Bacteriome and cancer

The most analyzed and metabolically important component of the human microbiome is the bacteriome, the collection of prokaryotes that reside on our mucosal and epithelial surfaces. The bacteriome can be altered by environmental factors, such as the host's diet, immune response, or use of antibiotics. The majority of our bacterial microbiome resides in the GIT and aids digestion, plays a major role in modulating the immune system through metabolites, such as short-chain fatty acids [2], and is a barrier to the proliferation of harmful pathogens [3]. Harmful alterations in the bacteriome, known as

dysbiosis, can induce carcinogenesis due to the proliferation of oncogenic bacteria and the effect of bacterial metabolites on the host, even in organs without their own bacteriomes [4–6]. This can be seen in colorectal cancer (CRC), hepatocellular carcinoma (HCC), lung cancer, breast cancer, and gastric cancer [4]. The effect that bacteria have on the host can be community-based or species-based; some bacteria were found to be enriched in certain cancers, while others were shown to have a causative role. For example, a dysbiotic bacteriome can lead to an increase in microorganism-associated molecular patterns (MAMPS), which can then lead to an innate immune response and the formation of host-derived and bacteria-derived reactive oxygen species (ROS) and reactive nitrogen species (RNS) that can damage host DNA [4]. Conversely, individual bacteria, such as *Helicobacter pylori*, can directly induce gastric cancer by causing epithelial injury, which leads to inflammation and later carcinogenesis [5]. *Fusobacterium nucleatum*, *Escherichia coli*, *Streptococcus gallolyticus*, and *Bacteriodes fragilis* have all been reported to be associated with CRC in humans [4]. The mechanisms, in which they induce carcinogenesis, include stimulation of the Wnt pathway via initiation of NF-kB signaling (*F. nucleatum*) [7] production of genotoxins, such as cytolethal distending toxin (*E. coli* and *Salmonella enterica*) [8], promotion of inflammatory cytokines (*S. gallolyticus*) [9], and breakdown of E-cadherin (*B. fragilis*) [4,10,11]. Pancreatic cancer has also been associated with a distinct bacteriome that is thought to contribute to the progression of oncogenesis through peritumoral immune suppression, thereby generating a tumorigenic environment [12]. The oncogene Kras, a major inducer of pancreatic cancer, is activated through inflammatory pathways, such as the binding of bacterial products like MAMPs and lipopolysaccharides (LPS) to Toll-like receptors (TLRs) on immune cells [13].This highlights the importance of the bacteriome in cancers with an important inflammatory component, such as liver and colon cancers, which have been shown to have decreased rates of carcinogenesis in germ-free mice [5,13]. Oral squamous cell carcinoma has also been associated with specific bacterial populations that differentiate it from non-tumor controls and may contribute to the carcinoma's pathogenesis [14,15]. A recognition of the many ways that the bacteriome can affect tumor progression may lead to innovative treatment options that have not yet been explored. In mice, for example, it has been reported that antibiotics may inhibit tumorigenesis by preventing the DNA methylation that occurs in cases of chronic inflammation [16]. An understanding of the bacteriome's role in cancer can help with the development of novel therapies and diagnostic techniques that may assist clinicians in treating cancer patients.

Virome and cancer

A less studied community is the collection of viruses that reside in the GIT, lungs, skin, nasal cavity, and oral cavity, which are known collectively as the human virome [17]. The human virome contains mainly human viruses and bacteriophages and alterations or additions to the virome have already been implicated in a variety of diseases, such as periodontal disease, cystic fibrosis, inflammatory bowel disease, HIV infection, urinary tract infections [18], sarcoidosis, and malnutrition [17]. There is also a multitude of viruses that can become components of the virome, temporarily or permanently, through infection and then either directly or indirectly induce carcinogenesis. Integration is a required stage in the life cycle of retroviruses. Integration may also occur with non-retroviruses via mechanisms such as homologous recombination. The majority of virus-caused human tumors, including most of the tumors caused by HBV, HPV, HTLV-1, and MCV, carry multiple viral integration events in their genomes [19]. In 2012, it was reported that 15.4% of worldwide cancers are caused by infectious agents, such as *H. pylori*, HPV, HBV, HCV, and EBV [20]. EBV was the first virus to be directly associated with a human cancer [21] when it was discovered that EBV induced Burkitt's lymphoma. It was later discovered that EBV also plays a role in the carcinogenesis of nasopharyngeal carcinoma [22], a subset of stomach cancers [23], and Hodgkin's lymphoma [24]. EBV, CMV, and HHV-8 have been associated with a variety of GIT cancers [23]. HPV is strongly associated with cervical cancer and moderately associated with head and neck cancers [25] and bladder cancer [17,23,26]. Chronic HBV virus and HCV virus infections are associated with HCC [23,27]. The mechanisms, in which each of these viruses interact with carcinogenesis, vary in terms of genomic alterations, mechanistic effects on cellular pathways, chronic inflammation, and the effect that bacteriophages might have on the bacterial community. In gastric cancers, EBV induces carcinogenesis through Nuclear Antigen 1 (EBNA1), Latent Membrane 2A protein, and encoded small RNAs (EBER) by enhancing cell survival, chemoresistance, and proliferation [4]. In HPV, the E6 and E7 viral oncogenes are expressed in all associated tumors [23] and downregulate the functions of p53 and Rb, respectively; Rb and p53 are key tumor suppressor genes that control the cell division cycle. Community-based viral oncogenesis has also been reported. It has been shown that colon virome diversity is altered in cases of CRC [18] and another study specifically described the virome diversity as increased in cases of CRC [28]. A hypothesized mechanism for community-based viral oncogenesis in CRC is that a few bacteriophages with a wide host range can indirectly promote carcinogenesis by lysing bacteria, allowing opportunistic, tumorigenic bacteria, such as *F. nucleatum*, to proliferate in the gut and become carcinogenic while allowing secondary opportunistic bacteria to establish themselves on a growing biofilm. Phages may play a role in biofilm development and oncogenic bacteria may then invade the epithelium and promote the transformation of tumor cells [18]. Another study indicated that

bacteriophages play a role in interspecies competition [29], which implies a role in dysbiosis as well. Interestingly, some phages may actually play a role in the prevention of cancer as they have been shown to have an inhibitory effect on cancer growth and have been implicated in anticancer treatments [30]. Although the direct viral effects on genetic mutagenesis have been previously studied, more research needs to be conducted on how the viral community as a whole may contribute to or prevent carcinogenesis through interactions with the bacteriome. A summary of the interactions between the bacteriome and virome in disease is represented below (Figure 1).

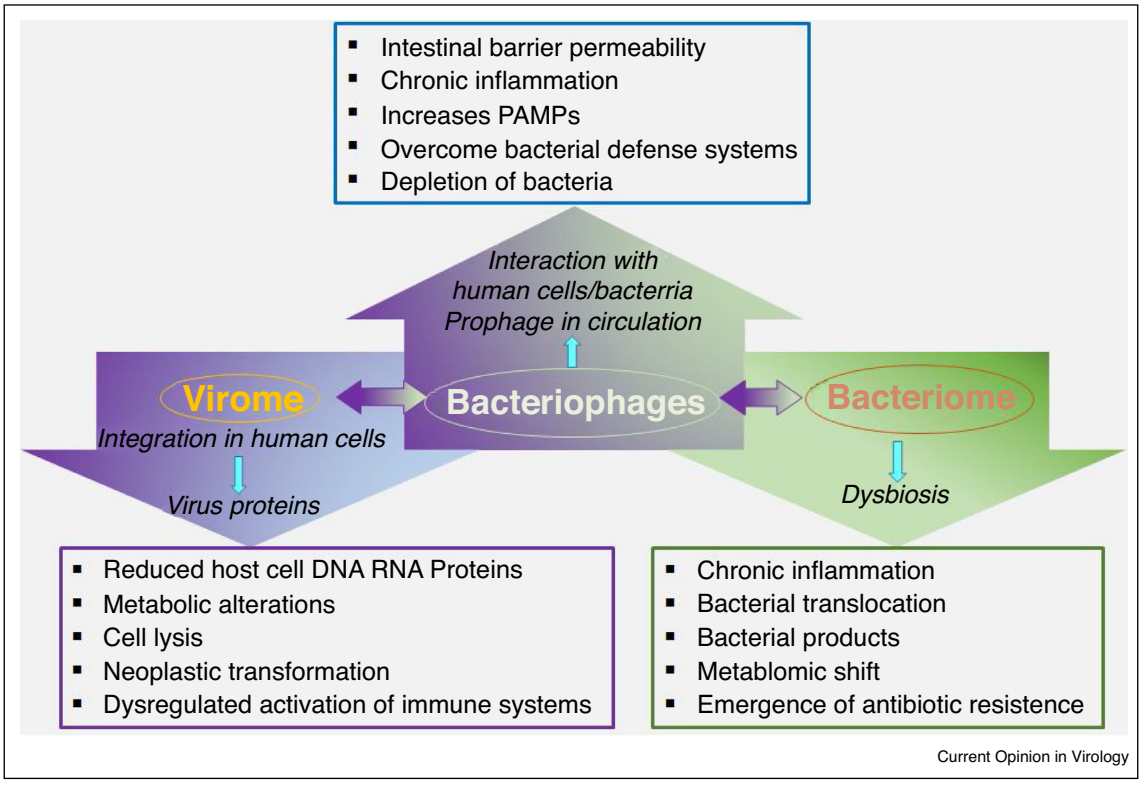
Bacteriome and HIV

The bacteriome's key role in modulation of the immune system and HIV's ability to impair it implies that HIV infection should have a reasonable effect on the bacteriome and *vice versa*. The gut bacteriome is different at each site of the human gut [31] (Figure 2) and, as a result, may interact differently with HIV infection. HIV does have measurable effects on the GIT, such as preferential depletion of CCR5 CD4 T-cells in the gut lamina propria [32], increased translocation of bacterial metabolites [33], and other gastrointestinal pathologies, such as diarrhea and inflammation [34]. It has been reported that HIV-infected patients with CD4 counts <200 had significantly decreased enteric bacteriome diversity, when compared to subjects with CD4 counts >200, and that OTUs belonging to the *Enterobacteriaceae* family, such as *Shigella* or related *Escherichia* species, were associated with low CD4 counts [34]. Previous cluster analysis showed that the bacteriome is distinct in HIV-positive patients when compared to HIV-negative individuals [31] (Figure 3).

Interestingly, certain bacteria may even play a protective role against HIV infection, such as *Ruminococcus callidus* and *Ruminococcus bromii* [34]. The translocation of bacterial products across damaged epithelial barriers that are characteristic of HIV infection may lead to chronic inflammation in peripheral tissues and systemic effects, even in patients on HAART without detectable viral loads [33]. Chronic immune activation is at least partially caused by circulating bacterial metabolites, such as LPS [35], that may have crossed the gut epithelial barrier.

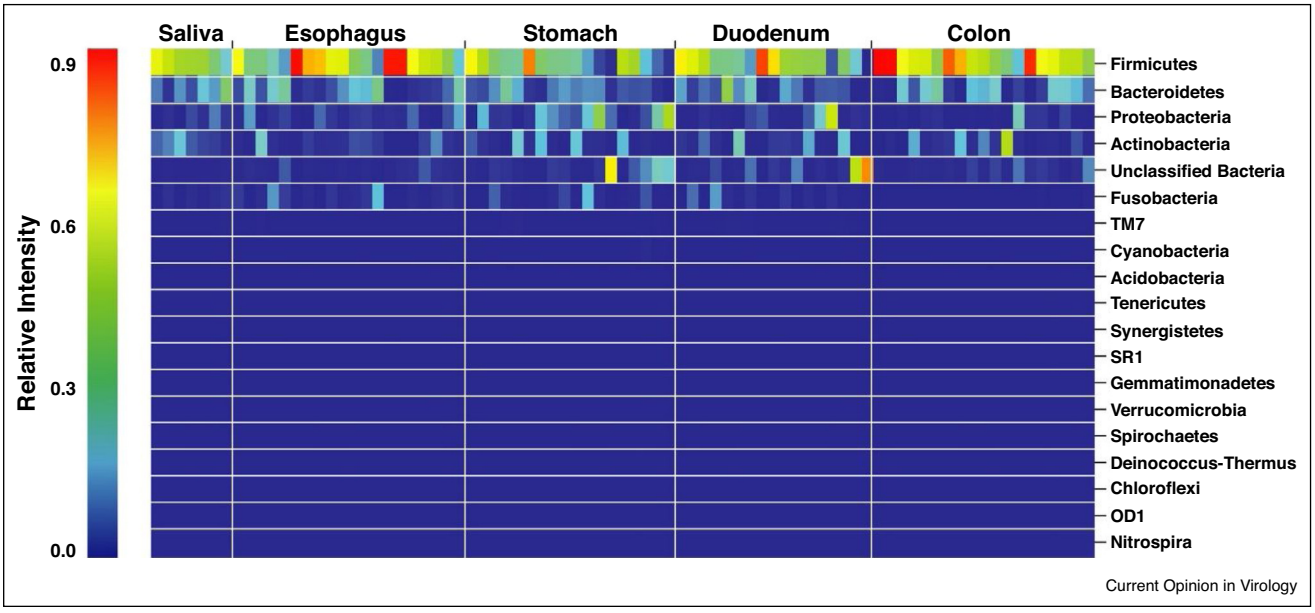
HIV infection also has an effect on microbiomes in other organs of the body as well. It has long been known that the lungs are significantly more susceptible to pneumonia after HIV infection and that HIV-infected individuals have decreased lung function following pneumonia, which is not seen in HIV-uninfected individuals [3]. It has also been suggested that the penile and vaginal

Figure 1



Ideal Partnership between Virome and Bacteriome in causing human disease.

Figure 2



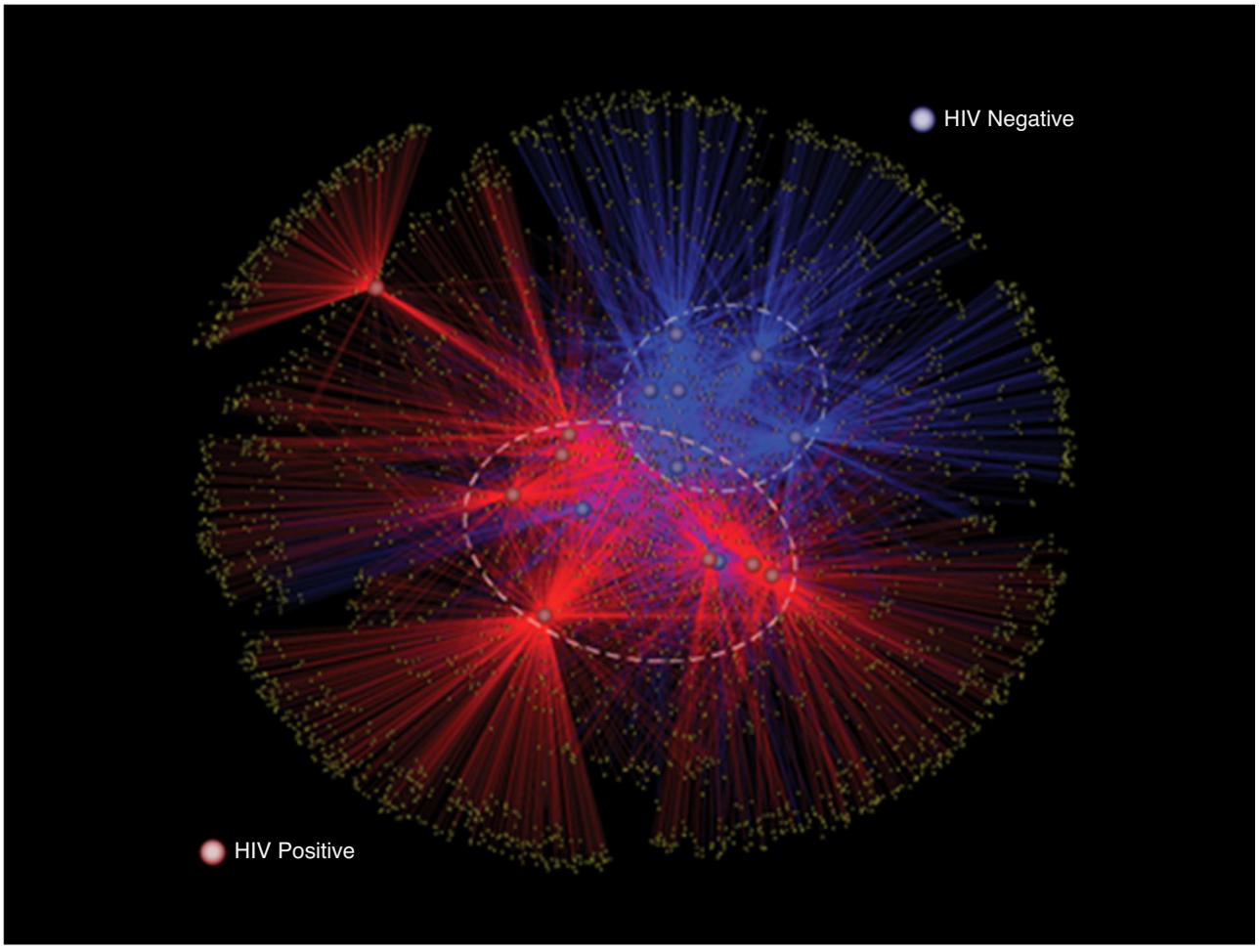
Heat map showing the 19 phyla and 498 genera that were found in samples. In the orodigestive tract, Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria are the major phyla. However, the bacterial diversity is different in each site. The small red bar presents high relative abundances around 90%, whereas the small blue bar presents relative abundances near zero (Oral Diseases, Volume: 22, Issue: S1, Pages: 73–78, First published: 25 April 2016, DOI: https://doi.org/10.1111/odi.12392. Used with permission from Wiley).

bacteriome has a marked influence on the effectiveness of transmission of HIV through sexual intercourse [3,36]. The oral cavity is also a crucial part of HIV infection as some of the most characteristic symptoms of HIV infection appear there very early on in the infection. These include Kaposi's sarcoma, oral candidiasis, oral hairy leukoplakia, necrotizing ulcerative periodontitis, and HPV lesions, which are all associated with either viral, fungal or bacterial infections that occur simultaneously with HIV infection. HIV-positive individuals have elevated salivary levels of *Streptococcus mutans*, total *Lactobacillus* species, and total *Candida* species when compared to HIV-negative controls [3]. The levels of *S. mutans* and *Lactobacilli* may be significant as they both play a role in the caries process and HIV-infected children have a higher rate of decayed, missing, or filled teeth than non-infected siblings [37], although this correlation was not seen in adults [38]. The effect of HAART on the microbiome and whether the microbiome normalizes after HAART is also an important clinical factor. HAART treatment seems to have a discernible effect on the microbiome: patients on HAART showed decreased levels of *Bacteroidetes* and *Firmicutes* and increased levels of *Protobacteria* were observed in Asian macaques, although the bacteriome normalized after two weeks of treatment [33]. *Lactobacillus*, which was reduced in SIV infection, normalized after one month of treatment [33]. It has been reported that HAART at least partially modulates the overall diversity of the bacterial microbiome back to pre-HIV levels [31]; however, more research still needs to be conducted on HAART's ability to normalize the human microbiome.

Virome and HIV

HIV infection is associated with a variety of other viral infections. For example, VZV tends to be reactivated in patients who are immunosuppressed due to HIV. HIV patients tend to lack immune responses to EBV and develop oral hairy leukoplakia. HIV is known to be synergistic with HHV-8 through induction of HHV-8 replication and HIV benefiting from HHV-8's ability to inactivate Rb. HIV and HHV-8 together contribute to the pathogenesis of Kaposi's sarcoma. Here, we will focus on the effect that HIV has on the viral community as a whole. It has previously been reported that HIV infection leads to an increase in enteric adenoviruses, but does not alter the bacteriophage population in humans [34,39]. In gorillas, Herpesviridae and Reoviridae were significantly elevated in SIVgor-infected gorillas, whereas Rhabdoviridae was significantly elevated in uninfected gorillas [40]. Pathogenic SIV infection of rhesus monkeys also showed an expansion of the enteric virome, including increases in parvoviruses and picornoviruses as well as adenoviruses, which were associated with enteritis and may play a role in AIDS enteropathy [39]. The expansion of the enteric virome can be controlled with proper vaccination, which

Figure 3



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Operational Taxonomic Unit (OTU) network in which the similarities and differences between HIV-positive and HIV-negative individuals is emphasized. Analysis using 454 pyrosequencing and QIIME indicated that the bacterial phylotypes are different in HIV-positive, as compared to HIV-negative, individuals and two separate clusters were observed (Oral Diseases, Volume: 22, Issue: S1, Pages: 73–78, First published: 25 April 2016, DOI: https://doi.org/10.1111/odi.12392. Used with permission from Wiley).

may help reduce the incidence of enteropathy in AIDS [41]. The viruses identified in the feces of primates have also been shown to be able to infect other tissues and enter the systemic circulation [39], likely due to the impaired intestinal epithelium that is a result of chronic HIV infection. It is possible that the altered enteric virome may be due to the inability of the host to fight against viral infections that it might normally contain due to depleted gut immunity. Although there has been much progress in determining the associations and mechanisms of the bacteriome and HIV in humans, the studies on the virome and its association with HIV/SIV are mostly primate-based. The research from non-human primates indicates that there are likely discernible differences in the total human virome after HIV infection. The evidence of expansion of the enteric virome shows that it would be worthwhile for more research to be conducted on the effect that HIV has on the human virome as well as the effect that HAART would have on reversing any changes in the virome.

Oral metabolome and HIV

Our group has also conducted a study on the altered metabolites found in the oral cavities of patients with HIV before and after HAART, compared to HIV-negative individuals. We were able to identify 16 metabolites that were differentiated based on disease status. There was only one metabolite that was statistically different between HIV-positive after HAART and the HIV-negative group, indicating that HAART may be able to mostly

normalize the metabolic profile of the oral cavity. Many of the metabolites identified in HIV-infected patients were associated with neurocognitive metabolism, which would explain HIV's key role in neurocognitive decline. It is possible that some of the elevated metabolites found in the oral cavity may be due to translocation of bacterial/virus products that are released systemically because of the damaged gut epithelium, as described above.

Conclusion

The intestinal phages raised intriguing questions about whether intestinal phage–bacteria interactions follow a traditional reciprocal predator–prey relationship (i.e. as phage abundances go up, host bacterial abundances drop, and *vice versa*), as observed in other ecosystems, such as the ocean. Dysbiosis of the bacteriome has wide-ranging effects, including increased gut epithelial permeability, chronic immune activation, and chronic inflammation. Altered bacterial diversity also plays a role in the pathogenesis of a variety of cancers through community-based and species-based mechanisms. The virome also plays a major role in cancer progression. Most of the research on viral influences on cancers are based on specific viral mechanisms that rely on inflammation, genotoxins, or oncogenes. Studies have shown that blood DNA virome contain 94 different viruses, including sequences from 19 human DNA viruses, proviruses and RNA viruses (herpesviruses, anelloviruses, papillomaviruses, three polyomaviruses, adenovirus, HIV, HTLV, hepatitis B, hepatitis C, parvovirus B19, and influenza virus) were found in 42% of the study participants [42]. Whereas, Merkel cell polyomavirus in 49 individuals, papillomavirus in blood of 13 individuals, parvovirus B19 in 6 individuals, and the presence of herpesvirus 8 in 3 individuals indicating diverse virome in human blood. There is a reason to believe, however, that the relationship between the bacteriophages of the virome and the bacteriome may be a factor in the progression of carcinogenesis in the gut and elsewhere in the human body. Bacteriophages might also play a key role in patients' dysregulated immune response to the mucosal-associated bacterial population. Intestinal commensal bacteria carrying prophage DNA produce infectious virions that facilitate interspecies competition [29] possibly contributing to dysbiosis. In HIV, the bacteriome is a key factor in the pathogenesis, transmission, and progression of the infection and more research should be conducted on the benefits of trying to normalize the bacteriome in order to help regulate altered immune activation and chronic inflammation in HIV-infected individuals. Although it has long been known that HIV acts synergistically with a multitude of viruses, HIV's effect on the total virome in humans is not as clear since most of the literature has focused on the SIV infection of non-human primates. It is possible that intestinal bacterial community composition can be dictated by phages, and thus phages likely have a strong influence on shaping the microbiota. This fact stresses the importance of incorporating the virome into future '-omics' studies.

Conflict of interest statement

Nothing declared.

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