Chapter

Fecal Virome Transplantation

Derek Lin and Henry C. Lin

Abstract

The gut virome consists of a large population of eukaryotic and prokaryotic viruses that have an emerging role in human health and disease. Growing evidence for the importance of the virome includes recent findings on fecal virome transplantation (FVT) that suggest FVT may have therapeutic potential for the resolution of dysbiosis and treatment of dysbiosis-related disorders. Most viruses in the gut virome are bacteriophages (phages), which have a well-established role in regulating bacterial communities across environments. Phages also influence health and disease by interacting directly with the host immune system. The full extent to which gut phages should be considered as both a target and a tool for microbiome modulation remains to be seen. This chapter will explore the current understanding of the gut virome and the therapeutic potential for FVT.

Keywords: dysbiosis, virome, bacteriophage, phage therapy, microbial therapeutics

1. Introduction

While the role of the bacterial community during fecal microbiota transplantation (FMT) has been the focus of extensive investigation, there has been substantially less examination of the viral community. The growing body of research on the viruses of the gut microbiome, referred to, herein, as the gut virome, points to their role as an important regulator of gut homeostasis [1–4]. This occurs through the modification of microbiome structure, composition, and function by gut bacteriophages [5–9], as well as through direct interaction between the enteric virome and the human immune system [4, 10–14]. In line with the gut virome's regulatory role, several recent studies have shown that fecal virome transplantation (FVT), a procedure similar to FMT albeit filtered to exclude intact fecal bacteria, has potential for resolving gut microbiome dysbiosis and restoring a healthy microbiota [15–18]. The full breadth of possibilities for FVT are only now beginning to unfold, but this emerging field of study has produced exciting findings that suggest FVT may be a versatile therapeutic treatment for multiple forms of dysbiosis. Not only has FVT been used effectively for clinical treatment of *Clostridium difficile* infection (CDI), but promising preliminary results suggest FVT has potential for resolving other dysbiosis such as those associated with diabetes and small intestinal bacterial overgrowth. In this chapter we will be reviewing the current state of gut virome research and discussing the clinical potential for FVT.

2. The gut virome

The gut virome consists of a robust and diverse community of eukaryotic and bacterial viruses, with bacterial viruses (herein referred to as bacteriophages,

or phages) estimated to make up between 90% [19] and 97.7% [20] of the membership of the gut virome. Approximately 10^{14} viruses, comprised of ~1200 virotypes, reside in the gastrointestinal tract at any given time [21], a population that is roughly 10 times that of gut bacteria but comparable in diversity [22, 23]. However, the ratio of phages to bacteria is approximately 1:1 in the infant gut suggesting the population changes over the course of development [24]. Like microbiome composition, virome composition is highly responsive to diet and when individuals are placed on the same diet, their viromes have been found to converge [25]. However, once established, the human gut virome has been shown to have high inter-individual variation [26], sufficient enough for viromes to be distinguishable between related individuals, such as between infants and mothers [27]. Individual viromes are also stable over time and approximately 80% of gut viruses have been shown to persist over a 2.5 year period [28]. At the population level, metagenomic analysis of viromes has demonstrated that there is a core of shared viruses among viromes within a population that can be used to distinguish between other geographically distinct groups [29, 30]. Recent findings by Manrique and colleagues have suggested that there is also a globally distributed set of core phages that are considered to constitute a "healthy gut phageome;" in part, because the prevalence of these phages is significantly decreased in the setting of inflammatory bowel disease (IBD; [31]. Specific phage community compositions and structures are associated with specific gastrointestinal and extraintestinal diseases including colon cancer [32], IBD [14, 33–36], rCDI [16, 37], and diabetes [15, 38].

3. Phages in the gut

As the dominant members of the gut virome, phages have been the focus of studies on the role of the gut virome in health and disease. Phages are ubiquitous viruses that are the most abundant biological entity in the world and can be found anywhere that bacteria can be found. Studying phages in the gut presents a number of difficulties. The first of which is that phages lack a universal marker, such as the 16 s rRNA gene in bacteria. Second, since phages depend on their bacterial hosts for reproduction and only 39% of bacteria in the gut can be cultured [39], many phages that are associated with the other 61% cannot be cultivated. This means that modern phage research largely depends on costly and labor-intensive viral metagenomics, which also presents challenges due to the immense genetic diversity of phages, the lack of a robust virus metagenomic classification, and still nascent use of bioinformatics to evaluate data set generated from viral metagenomic analysis. Much phage research has revolved around the practice of phage therapy, which has been used for over 100 years in some Eastern European Countries to treat single strain bacterial infections. The emergence of antibiotic resistance has led to phages gaining recent attention for their potential as an alternative to antibiotics [40]. In phage therapy, patients are administered solutions of individual phage strains, or multiple strains (i.e. phage cocktail), which are selected through *in vitro* screening for their specificity to the single bacterial agent causing the infection and for their effectiveness in eliminating that one bacterial species. Much of the interest in phage therapy rather than antibiotics is based on the specificity of phages to target a narrow host range, allowing for the targeted elimination of a bacterial pathogen while leaving commensal bacterial members of the microbiome intact, and the ability of phages to self-propagate upon infection of their bacterial host.

In general, there are two types of phages: lytic and temperate. Lytic phages reproduce via the lytic cycle and temperate phages use the lysogenic cycle (**Figure 1**). Conventional phage therapy uses lytic phages because in the lytic

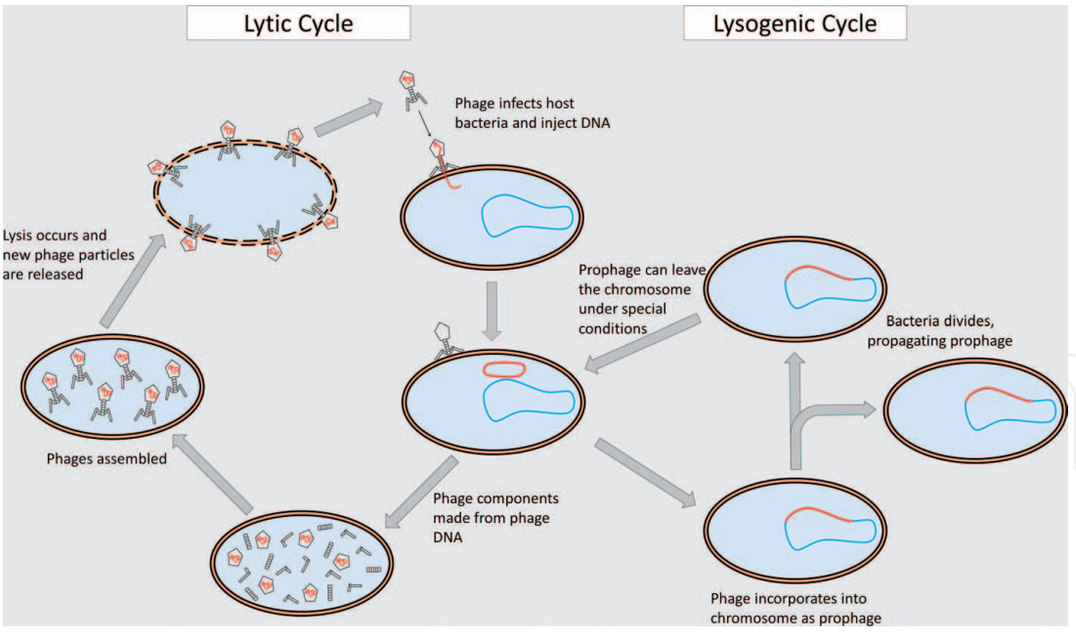

Figure 1.
Reproductive lifecycles of phages.

lifecycle, phages infect a bacterial host, hijack the host machinery for replication of viral progeny, and eventually lyse the host cell and the release of novel phage progeny. In the lysogenic lifecycle, a temperate phage infects a bacterial host and integrates its viral DNA into the bacterial chromosome as a prophage. This process does not always end in cell lysis, instead the prophage can reproduce by propagating with the bacterial chromosome during replication. Harmful environmental stimuli in the gut, such as oxidative stress [41], antibiotics [42], or other unfavorable conditions for the bacterial host [43], can result in the induction of the prophage into the lytic cycle, thereby resulting in the lysis of the bacterial host and release of novel phage progeny. However, Lysogenic (temperate) phages are generally not used in phage therapy because lysogeny is a mechanism for bacteria to exchange DNA so lysogenic phages carry the potential for propagating genes for pathogenesis.

While lytic phages are largely seen as parasitic to their bacterial hosts, temperate phages and their host bacteria have a much more complicated relationship. Temperate phages are important drivers of bacterial evolution [44], in part through their role in horizontal gene transfer between bacterial hosts. Temperate phages are common in the gut and studies have found that a large proportion of bacteria in the microbiome have temperate phages incorporated into their genomes as prophages [21, 45]. For the bacterial host, carrying prophages has several fitness benefits. Prophages encode genes for metabolism, antibacterial resistance, and toxin production (for example, shiga toxin production) [9, 46], thereby conveying functional genes for survival to their bacterial hosts upon integration with the bacterial chromosome. Prophages also protect their hosts from infection by lytic phages through superinfection exclusion [47]. Phage-mediated horizontal gene transfer between bacterial hosts increases rates of genetic recombination and diversification of phage-encoded genes in the gut [48].

Composition, structure, and function of the gut virome contributes to health in a number of ways [49], as reviewed by Mukhopadhya and colleagues [50]. The coevolution between phages and their bacterial hosts is a well-established mechanism for driving the development of microbial communities across environments [44]. This is also the case in the gut environment where phages are thought to modulate the microbiota and, in turn, affect human health. A longitudinal study of

gut microbiome and virome composition in healthy infants found that expansion of gut bacterial species was accompanied by contractions and shifts of gut phage populations, suggesting that phage predation of targeted bacteria may help drive the development of a healthy infant gut microbiome [51]. Conversely, in the setting of dysbiosis, changes in the gut phage population have been shown to precede the onset of type 1 diabetes in children [38]. Phages are also thought to form a protective barrier in the mucosa of the gastrointestinal epithelium, thereby providing the host tissue with non-host-derived defense against pro-inflammatory gut bacteria [52]. Experimental evidence suggests that they do this by using their Ig-like domains expressed on the viral capsid to attach to the glycan molecules of the host's mucin glycoproteins. Growing evidence now implicates a role for phages of the mucosa in states of dysbiosis, which have been characterized by an increased richness and abundance of the mucosal temperate phage population [9, 14, 34, 35, 53]. These changes in the phage community is opposite that of the bacterial community in which decreased richness and diversity characterize dysbiosis.

The virome also influences health through direct interaction with the human immune system by triggering both pro- and anti-inflammatory action [4, 10–14]. Phages are capable of activating TLR9-mediated IFNγ, a pro-inflammatory pathway that exacerbates intestinal colitis [14]. Conversely, phages can also ameliorate inflammation through TLR3- and TLR4-mediated interferon-β activation [11]. Several studies have found elevated abundance of phages in the mucosal surfaces of patients with IBD [36, 53]. Other studies have found an expansion of phages from the order *Caudovirales* in the setting of inflammatory bowel disease [34, 54, 55]. Norman and colleagues speculate that phages may contribute to, or be a biomarker for, inflammation and dysbiosis in the gut. Collectively, these studies indicate that phages have an important role in gastrointestinal disorder and potentially, in the corrective response to dysbiosis.

4. Therapeutic potential for FVT

In the setting of FMT, a large population of phages is transferred from the FMT donor to recipient. Feces contain approximately 10^9 virus-like particles per gram, a density similar to that of fecal bacteria, and phages account for upwards of 90% of all fecal virus-like particles [19]. It follows that the large transfer of fecal phages during FMT could have a physiological effect on the FMT recipient. In attempting to examine the role of fecal phages during FMT, several recent studies have not only characterized a state of virome dysbiosis in the setting of recurrent *C. difficile* infection (rCDI), but also have shown that recovery is associated with uptake of a healthy virome from the FMT donor [16, 37, 56]. A study of one FMT patient found that the patient had adopted the donor's phage community after 7 months, even when the patient's microbiome maintained a dysbiotic composition. The microbiome resembled that of the healthy donor a year later [16]. This observation that the adoption of a 'healthy' phage community precedes resolution of dysbiosis may suggest a role for phages in promoting and maintaining a healthy microbiome. This possibility is further substantiated by Zuo and colleagues who found that successful recovery from rCDI after treatment with FMT was associated with a high level of colonization by the donor's phage community in the recipient's enteric virome [37]. Another study showing long-term stability of the FMT recipient's virome found that the donor's phage community maintained colonization of the recipient 12 months after treatment [56]. Similar findings have been observed in clinical trials for FMT as an intervention for pediatric ulcerative colitis [57].

Additional evidence for the active role of phages during FMT comes from studies on fecal virome transplantation (FVT) showing that the sub-bacterial fraction of a FMT (i.e. bacteria removed) can manipulate the composition and structure of a recipient's microbiome [15, 18, 58]. One clinical study found that a fecal suspension that was filtered to remove bacteria, while leaving phages and other sub-bacterial particles intact, was sufficient for effective clinical treatment of rCDI and restoration of a healthy microbiome [58]. Similarly, Kao and colleagues found that a sterilized fecal filtrate was sufficient for treating rCDI [59]. Using another clinically relevant model of dysbiosis, Rasmussen and colleagues demonstrated that a FVT from lean mice was effective at reducing weight and symptoms of diabetes type 2 in obese mice fed a high-fat diet [15]. The investigators also showed that the FVT was able to increase bacterial diversity in the microbiome to the levels in lean mice. The ability for FVT to modulate microbiome composition is further supported by evidence showing that a FVT from high-fat diet-fed obese mice was sufficient for driving microbiome composition of healthy mice towards that of the high-fat diet donor [18]. The investigators also found that a FVT was sufficient for reducing small intestinal bacterial overgrowth (i.e. excess bacterial density in proximal small intestine) in obese mice to the level of healthy controls. In another recent study, investigators found that FVT also prevents necrotizing enterocolitis in preterm piglets [60]. Additionally, there is some speculation that the gut virome has a role in the "super-donor" phenomenon observed during FMT [61]. Collectively, these early studies demonstrate the therapeutic potential for FVT in multiple settings of dysbiosis.

5. Dynamics of FVT-based modulation of the microbiome

The mechanisms through which FVT modifies the recipient's gut microbiome is the subject of ongoing investigation and is likely the result of complex community interactions between donor phages and recipient bacteria, all of which is likely heavily influenced by the host gut environment. Temperate and lytic phages exhibit different population dynamics within microbial communities, and administration of individual strains of exogenous phages into the gastrointestinal tract of mice has been used to study these dynamics [5, 6, 62]. In a gnotobiotic mouse model where the gut is colonized by a defined community of resident gut bacteria, the administration of monocultures of lytic phages exhibiting a narrow host range can reduce populations of their host bacteria through predation [5]. It was also observed that reducing targeted host bacteria subsequently leads to a cascading effect in which populations of non-host bacteria in the microbiome are affected through inter-bacterial interactions. This effect propagated throughout the gut the microbiota with far-reaching consequences for the composition, structure, and function of the microbiota. Additionally, there is some evidence that a phage therapy approach has the potential to control or eliminate bacterial pathogens, such as *Enterococcus faecalis*, in the gut [63]. These studies provide models for studying basic phage-bacterial dynamics in the gut, particularly 'kill-the-winner' population dynamics where lytic phages act as predators leading to a suppression of their bacterial hosts and opening of new ecological niches for non-host bacteria.

Since both temperate and lytic phages are transferred to the recipient during FMT and sustained in the recipient's virome afterwards [17], it is likely that multiple population dynamics are at play in the setting of FVT. In a study using gnotobiotic mice with a defined microbiota, administration of a FVT from human feces resulted in a cascade of changing abundance of different gut bacteria that modeled

primarily that of temperate phage-bacteria dynamics [62]. In another study by Bao and colleagues, the investigators found that administration of lytic or temperate phage monocultures into the gut of healthy mice modulated the microbiome by changing relative abundances of host and non-host bacterial populations at both phylum and genus level [6]. Of note, in this particular study, lytic phages promoted a beneficial gut environment while temperate phages promoted conditions that would enable disease to occur. Other co-evolutionary phage-bacteria dynamics that have been observed in microbial communities include 'piggyback-the-winner,' 'arms-race,' and 'kill-the-relative' dynamics, which are reviewed in detail elsewhere [2, 64]. Collectively, these dynamics are thought to contribute to the onset and maintenance of states of dysbiosis in the microbiome and are therefore also likely to have a role in recovery from dysbiosis in the setting of FVT. In the setting of rCDI, it is unclear whether exogenous phages with a broad host range down-regulate *C. difficile* populations or whether they promote a healthier microbiome with less ideal conditions for *C. difficile* colonization.

6. Safety considerations for FVT

While therapeutic application of FMT has been explored in many settings of dysbiosis [65–68], current clinical guidelines recommend that FMT should only be used as a last resort for rCDI due to the various safety concerns [69]. Much of the risk of FMT comes from the transfer of bacteria into an immuno-compromised recipient and the potential of inducing an unanticipated bacteria-driven phenotype (e.g., obesity). Accordingly, FVT may be associated with less risk due to the removal of intact bacteria prior to transplantation. However, since viruses are also capable of eliciting a pro-inflammatory response [12, 14], more research needs to be done to better understand how FVT interacts with the recipient host.

Safe clinical application of FVT will also require a deeper understanding of the viruses that comprise the gut virome. Numerous disease-causing viruses reside in the gut including herpesvirus, papillomaviruses, and hepatitis viruses. Sequencing of the virome has revealed numerous other viruses including bocaviruses, entero-viruses, rotaviruses, and sapoviruses [28]. Many of these viruses have yet to be characterized and their function in the gut is unknown. Given the potential for infection by eukaryotic viruses, a thorough screening of the donor virome must be done to ensure that no harmful eukaryotic viruses are transferred into the recipient. The metagenome of the virome should also be screened since phages can encode genes for virulence factors (e.g., diphtheria toxin, shiga toxin, and botulinum toxin) and antibiotic resistance (e.g., β-lactamases) [70, 71].

Overall, the removal of bacteria is likely to make FVT a safer option than FMT. However, FVT still has safety considerations that must be better understood and effectively taken into account.

7. Conclusion

The emerging field of research focused on the gut virome is still in its infancy, in part due to the difficulty of studying viruses in the gut environment. However, similar to the field of microbiome research, recent work on the gut virome demonstrates how previously overlooked inhabitants of the gut have a profound influence on, and are in fact inseparable from, health and disease. In the setting of FMT, the emerging association between uptake of the donor's phage community and clinical outcome suggests that fecal phages may have an important but not yet fully

characterized role in successful treatment of rCDI. Whether FVT will offer a safer or more effective alternative to FMT remains to be seen. We still have yet to determine the full therapeutic potential of FVT, but the promising preliminary findings on FVT suggest it may provide new treatment options for dysbiosis and dysbiosis-associated disorders. Collectively, these recent advances argue for more attention to be given to FVT as a therapeutic tool for microbiome modulation and to the gut virome as a therapeutic target.

Acknowledgements

This work was supported, in part, by the Winkler Bacterial Overgrowth Research Fund.

Conflict of interest

The authors have I. P. rights in related areas.

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