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Bacteriophages and Intestinal Microbiome in Gastrointestinal Health

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Abstract

Bacteriophages, or phages, are viruses that infect and reproduce within bacteria. Bacteria are the most abundant microorganisms on Earth, and the most studied are a type of virus that infects *Escherichia coli*. Originally, the production of encoded toxins was the most relevant aspect; however, currently, the encoding of genes and their contribution to various aspects of bacterial pathogenicity are more prominent, including adhesion, invasion, and immune evasion. Furthermore, they disseminate virulence genes within bacterial populations, contributing to bacterial pathogenesis through unique properties, containing pathogenic components, and the induction of prophages via gene amplification, upregulation of transcription, and mediated lysis.

Keywords: *Bacteriophages (Phages); Gut Microbiome (GM); Fecal Microbiota Transplantation (FMT); Fecal Virome Transplantation (FVT)*

Introduction

Bacteriophages (Phages) have become promising candidates for therapeutic intervention against antibiotic-resistant pathogens. The alarming increase in antimicrobial resistance (AMR) among drug-resistant pathogens has been attributed to the ESKAPEE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* sp., and *Escherichia coli*) [1]. Phages study is a rapidly growing area of research. Discovered by Frederick Twort and Felix d'Hérelle at the beginning of the 20th century, Phages offer unique possibilities in relation to the dynamics of bacterial ecosystems [2]. They can possess either DNA or RNA, configure bacterial populations, and influence ecosystems. Given their ability to eliminate infections, the concept of phage therapy has been developed. Their unique properties, such as bactericidal activity, host specificity, potency, and biocompatibility, make them ideal candidates for therapeutics. This includes biomedical and pharmacological advantages, as well as their remarkable potential for modification, improvement, and application [3]. Of the 101,717 search results in the PubMed database, 163 clinical trials were identified, revealing a dynamic panorama of research activity between 1965 and 2024. There are approximately 1,031 bacteriophages, more than all bacteria combined. To understand the progress that needs to be made in the West, only 2,925 phage genomes and 370,000 bacterial genomes have been assembled [4].

Characteristics of phages

There are thousands of varieties that infect only one or a few types of bacteria or archaea. Some examples are Inoviridae, Microviridae, Rudiviridae, and Tectiviridae. Like all viruses, phages are simple organisms with a core of genetic material (nucleic acid) surrounded by a protein capsid. The nucleic acid can be DNA or RNA, and can be double or single stranded. During infection, a phage attaches to a bacterium and inserts its genetic material into the cell, following a lytic (virulent) or lysogenic (attenuated) cycle. Alfred Day Hershey and Martha Chase used the T2 bacteriophage in a famous experiment. They demonstrated that only the nucleic acids of the phage molecules were necessary for their replication within bacteria [5].

How to obtain bacteriophages in the laboratory?

Cultures are obtained by infecting bacterial cells. The phage can be isolated from the resulting bacterial culture plates. Virus or phage cultures require host cells to multiply [6].

Bacteriophages and the gut microbiome

It is a fact that phages influence the gut microbiota (GM). And, undoubtedly, they play a role in fecal microbiota transplantation (FMT), as they are part of the prognosis of the process. Authors use metagenomics to guide the study of phage populations in patients with ulcerative colitis. They observed that their behavior is similar to bacteria, being stable, exhibiting dysbiosis (active disease), modulated by antibiotics and FMT [7]. This suggests that tracking phages is useful for identifying solutions to the disease. They are considered modulators of the intestinal ecosystem, relating them to gastrointestinal diseases and the efficacy of FMT. The interactions between phages and the GM are receiving increasing attention due to the importance of this pairing. Phages are considered a dark matter because 80% of them have not been characterized [8].

Bacteriophages and fecal microbiota transplantation

Various methods have been used to modulate the GM for the benefit of the human host. Among them is FMT. Generally, the incidence of bacteria, rather than the virome, is examined due to the difficulty in sequencing the communities. It has been suggested that Phages regulate GM homeostasis, linked to the immune system. Their transfer in FMT is crucial in maintaining the ecological balance of the GM with the bacteria [9]. FMT has been used successfully in intestinal dysbiosis, although it is not universally accepted. Therefore, in this article [10], two processes are defined: 1) the administration of a bacterial cluster and 2) the virome. This minimizes heterogeneity.

Phages in bacterial pathogenicity

Phages penetrate bacteria through their cell wall, releasing viral genetic material and, through replication, releasing daughter virions, which impact surrounding cells. They interact with host bacteria within the GM, possessing effects on health. These interactions are targeted for their potential health effects [11].

Pathogenesis: Phages are part of the virulence of numerous pathogens, contributing through the encoding of structural genes (exotoxins). Present in almost all facets of pathogenicity, from adhesion and immune evasion to transmission, they possess unique properties that allow them to contribute to pathogenesis through mechanisms other than transduction [12].

Bacteriophage therapy: Twort and d'Hérelle conducted phage treatment, but were unsuccessful. The process was abandoned, except in Eastern Europe. Research was restarted in the West due to bacterial resistance. This is the case in the study by Palma M., *et al*. [13], who conducted a comprehensive review of phage therapy, using novel therapies, reporting that transplantation is safe in preclinical trials, preserving the beneficial GM. The authors also point out that the optimization of dosage, sample size, infectious multiplicity, resistance potential, kinetics, frequency, and patient-specific factors must be taken into account. They conclude that established practices in countries like Poland and Georgia further demonstrate its clinical viability.

Fecal microbiota transplantation (FMT): Its efficacy is related to the grafting of bacteriophages from healthy donors to recipients. Their mechanism of action is not fully understood. Taxonomic, functional, and lifestyle changes occur in the composition of the recipient's phagome, which should be further characterized in the future. Furthermore, because the bacteria are obtained by centrifugation, the number of phages could be reduced [14]. Now, what happens in patients with *Clostridioides* when they undergo phage therapy? Clinical studies have shown that FMT is a promising treatment for recurrent and refractory CDI, with a cure rate exceeding 90%. However, the mechanisms underlying its efficacy are largely unknown. FMT is considered an effective therapy for recurrent *C. difficile* infection. However, its safety is a concern because deaths caused by antibiotic-resistant bacterial infections have been reported after FMT. Therefore, a novel therapy with new generation phages developed from metagenomic data has been described [15].

Components of FMT: The components of FMT are complex and include live and dead bacteria, as well as viruses, bile acids, chemical molecules, and proteins. It is unclear whether some or all of them are necessary for the clinical efficacy of FMT. Fecal virome transplantation can induce phenotypic and microbiome improvements in various diseases. It has been assumed that live bacteria are necessary for FMT to function, as well as the virome, mycobiome, and other components of the GM [16].

Intestinal virome alterations following fecal microbiota transplantation in other diseases

In inflammatory bowel disease, a 54% clinical response and 37% overall response were reported; the fecal and mucosal virome showed a greater abundance of Caudoviral bacteriophages compared to healthy controls [17]. Meanwhile, another study investigated the transfer of viral communities during FMT, revealing numerous viral lineages in a patient with ulcerative colitis; and 32 different viral contigs from the donor [18].

Fecal virome transplantation (FVT)

The fecal virome transplant (FVT) that uses filtered stool containing intact phages, but not bacteria. FVT may offer a novel and promising therapeutic approach for metabolic diseases, warranting further validation through basic and clinical research. While the GM was previously thought to play a predominant role, it has been determined that phages exhibit surprisingly similar characteristics to the donor after FVT, with minimal modifications over time. Bacteria undergo these alterations over a longer period. Therefore, FVT alone is capable of producing changes in GM more effectively than bacteria [19].

Conclusion

- Metagenomic phages can alter the gut virome, though the mechanism by which this occurs is unknown.
- FMT is not only attributed to the restoration of a healthy GM but also involves the modulation of the gut virome.
- Viral metagenomics methodology has limitations, such as difficulties with DNA amplification bias, the challenge of distinguishing between true viral sequences and bacterial DNA, and the inability to taxonomically classify most gut viruses.
- Access to high-throughput sequencing of the gut virome, along with the assessment of its interaction with other GM components, will further enhance our understanding of the importance of bacteriophages and their role in FMT.

Conflicts of Interest

The authors declare that do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

Declaration on the Use of Artificial Intelligence

The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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