Microbiota & Diseases

REVIEW

# Phage: Future treatment direction for inflammatory bowel disease patients

Xiaotong Shen, Airu Liu, Xiaonan Liang, Xiaolan Zhang*

Gastroenterology Department of East Hospital, The Second Hospital of Hebei Medical University, Hebei Key Laboratory of Gastroenterology, Hebei Institute of Gastroenterology, Hebei Clinical Research Center for Digestive Diseases, Shijiazhuang, Hebei, China

**ABSTRACT**

Inflammatory bowel disease (IBD) is characterized by tissue damage resulting from uncontrolled innate and acquired immune responses. It is an autoimmune disease, including ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis (IC). The etiology of IBD is complex, and its clinical treatment faces significant challenges, necessitating urgent exploration of new treatment methods. Emerging evidence indicates that gut microbiota and IBD interact in the occurrence and development of diseases, emphasizing the importance of restoring gut microbiota imbalance. Phages have gained attention due to their potential to their potential to act on gut microbiota, offering advantages such as high efficiency, easy access, and ability to disrupt bacterial cell structures. Consequently, research into how phages interact with bacteria and their potential as a novel treatment for IBD has become a recent hotspot. Phages regulate intestinal inflammation by activating the immune system. Previous studies have observed an increase in the abundance of *Caudovirales* phages in IBD patients. Latest research reveals that special combinations of bacteriophages can effectively improve the symptoms of IBD model animals. This article reviews the interaction mechanism between phages and gut microbiota as well as the related research progress in IBD. The selection of articles retrieved on PubMed based on phage and Inflammatory bowel disease.

**Key words:** Inflammatory bowel disease, Ulcerative colitis, Crohn's disease, gut microbiota, phage, treatment,

## INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis (IC), is a chronic, recurrent, nonspecific inflammatory disease of unknown origin. UC and CD predominantly affect young indivaduals, with high incidence rate reported between 20–49 years old; the high incidence age of CD is 18–35 years old for CD in China.[1] Epidemiological data show that the IBD morbidity has increased year by year, especially in some non-western developing countries, such as Southeast Asia, Africa, South America and other countries.[2–4] The pathogenesis of IBD is complex, involving various factors such as genetic susceptibility, immune, gut microbiota and other factors, among which the imbalance of gut microbiota is considered to be the key event in the occurrence and development of IBD.[5,6] moreover, dietary changes, antibiotic use and gender are involved in host-microbe interactions.[2]

The human gut harbors an extensive and diverse microbial community, comprising bacteria, fungi, archaea, viruses, and other microorganisms, with an estimated number of approximately 100 trillion.[7,8] The composition and distribution of microorganisms in different intestinal segment are also very various. Eckburg *et al.* identified over 1000 bacteria species in the

***Corresponding Author:**
Corresponding Author: Xiaolan Zhang, Gastroenterology Department of East Hospital, The Second Hospital of Hebei Medical University, Hebei Key Laboratory of Gastroenterology, Hebei Institute of Gastroenterology, Hebei Clinical Research Center for Digestive Diseases, Shijiazhuang, Hebei, China. E-mail: xiaolanzh@126.com
Received: 2 January 2024; Revised: 3 April 2024; Accepted: 28 May 2024
https://doi.org/10.54844/md.2023.0434

intestinal tract, primarily including *Bacteroidetes, Firmicutes, Proteobacteria, Actinomycetes* and so on.[9] Imbalance in the gut microbiota can trigger IBD, and conversely, IBD can also affect the composition of the gut microbiota. Studies have shown alterations in bacterial diversity and abundance in IBD patients, notably characterized by reduced levels of *Firmicutes* and increased levels of *Proteobacteria*.[10–12] Gut microbiota can regulate the proliferation and apoptosis of intestinal epithelial cells, restrain the excessive reproduction of pathogenic bacteria, to maintain intestinal homeostasis.[13] However, when the gut microbiota is out of balance, the function of immune cells will be affected, and intestinal mucosal barrier may also be destroyed, which may lead to IBD, colon cancer, irritable bowel syndrome and other diseases.

Phages, also known as bacteriophages, are a type of virus that rely on parasitizing bacteria and exhibit high host specificity, constituting about 90% of the intestinal viruses.[14,15] They consist of nucleic acid and a protein capsid and can be classified into temperate phages and lytic phages based on their reproductive characteristics. Temperate phages integrate their own genetic materials onto the host bacteria chromosomes or exist in the host bacteria cytoplasm in the form of plasmids. With the replication of the host bacteria, the genetic materials are transmitted downward, remaining stable and not undergoing breakdown.[16] On the other hand, toxic bacteriophages first attach bacteriophage particles to the host cell, inject their genetic material into the host cell, stop the synthesis of host components, replicate the bacteriophage genome, produce the required protein shell and assemble new bacteriophage particles before finally release the offspring bacteriophage particles to infect other bacteria.[17,18]

Phages have attracted people's attention due to their ability to act on gut microbiota. Phages can affect the number and behavior of host bacteria as well as mediate gene transfer between bacteria. Phages can impact human health through bacteria lysis or affecting metabolism and immune system. Adjusting the relationship between phages and bacteria can maintain the health of the body, and even reverse the disease. In general, phage is a kind of virus parasitic on bacteria, which could transfer genetic material by splitting bacteria or integrating genetic material into host bacteria.[19,20] In recent years, phages have drawn our attention because of their easy access, high efficiency, and other characteristics. How phages interact with bacteria has become a research highlight.

This paper explores the interaction between phages and gut microbiota, the mechanism of phages regulating inflammatory bowel disease and the specific effects of phages therapy in detail. The relationship between phages and gut microbiota as well as the latest application in IBD were further discussed, providing reference for phages as a drug for the treatment of IBD.

The selection of articles retrieved on PubMed based on phage and Inflammatory bowel disease, with no restrictions on the year of publication, although the most prominent articles are those published after 2017. A total of 49 articles were selected and included in the review.

## INTERACTION BETWEEN PHAGES AND GUT MICROBIOTA

### *Effects of phages on intestinal bacteria*

Research has shown that bacteriophages primarily affect the gut microbiota through the following aspects [21] :(i) Phage specific lysis sensitive bacteria, Cepko Leah *et al.*[22] found that *Myoviridae phage PDX* can selectively kill disease-related Enteroaggregative *Escherichia coli* (EAEC) without causing imbalance of gut microbiota. (ii) Phage affects gut microbiota through horizontal gene transfer horizontal gene transfer (HGT), The mechanisms of phage HGT include specialized transduction, generalized transduction, lateral transduction, molecular piracy, and others.[23] The highly mobile pathogenicity island of *Staphylococcus aureus* (SaPIs) is particularly suitable for the packaging and transfer of specific *staphylococcal phages*.[24] (iii) Phage encodes virulence factors of bacterial populations and transmits toxin coding genes of diphtheria, cholera, dysentery, scarlet fever and other diseases among strains. Research shows that *filamentous phage* CTXφ is integrated at the decomposition site Dif1 of the two large dimers of *Vibrio cholerae* chromosomes, leading to the genetic diversity of cholera epidemic strains and affecting the release of cholera toxin by *Vibrio cholerae*.[25](iv) Phage participates in bacterial metabolism regulation and affects the production of metabolites by altering the gene structure of host bacteria and the expression of related metabolites. (v) Other functions: after affecting the number of host bacteria, bacteriophages may influence the growth of other bacterial populations through the interaction between gut microbiota. Hsu Bryan *et al.*[26] discovered that bacteriophage T4 can reduce the number of *Escherichia coli*, thereby inhibit the growth of *Bacillus fragilis* and promote the growth of general *Bacteroides*.

### *Defense measures taken by intestinal bacteria against phage invasion*

The gut microbiota can also antagonize bacteriophages through various mechanisms, such as altering or hiding corresponding receptors, modifying or destroying phage DNA in multiple ways.[21] For example, *Vibrio cholerae* reduces the expression of O1 antigen by regulating the expression of necessary genes to avoid phage adsorption;[27] additionally, Ongenae *et al.* hypothesized that bacteria might evade phage attacks by shedding cell

walls and transforming into bacteria without cell walls.[28]

The immune system degrades bacteriophage DNA and plays a defensive role, including restriction endonuclease modification system, clustered regularly interspaced short palindromic repeats (CRISPR)-Cas systems, *etc.* The restriction endonuclease modification system, an innate immune system of prokaryotes, consists of restriction endonuclease nuclease and methyltransferase. Methylation modification of bacteria's own DNA base makes it not be recognized and cut by its own restricted endonuclease, while the DNA of the entered bacteriophage is usually not methylated, but is recognized and cut by the restricted endonuclease, limiting the proliferation of bacteriophages.[28] The Cyclic oligonucleotide-based signaling system (CBASS) system is an immune defense system widely present in bacteria and archaea, comprising cyclic gmp-amp synthase (cGAS) and downstream protein effector molecules. These effector proteins can kill bacteria infected by bacteriophages or inhibit bacterial growth, thereby preventing bacteriophage proliferation. The bacterial immune defense against phage infection mediated by the CBASS system, also known as the abortive infection process, initiates programmed cell death of infected cells before phage replication, thereby protecting other cells in the bacterial population. This process involves the molecular mechanism by which bacteria move from sensing bacteriophages to initiating individual suicide, ultimately leading to the development of immune defense against bacteriophages in the bacterial population.[29] Phages maintain the stability and diversity of gut microbiota by interacting with their host bacteria.

## PHAGES AND IBD

The gut virome, primarily composed of bacteriophages, plays a crucial role in influences gut homeostasis and pathogenic conditions through its interaction with the gut bacterial community. Many phages exist in a lysogenic or latent state remaining integrated as prophages within the host bacteria.

### *Phages alterations in IBD*

It is speculated that there are $10^{13}$ virus particles in each human body, involving phages and eukaryotic viruses mainly detected in the intestines.[30] There are differences in the gut virus group between healthy individuals and IBD patients. In healthy individuals, the gut virus group is mainly composed of *Caudoviricetes* and *Malgrandaviricetes*.[31] Due to the different composition of individual gut virus groups, the conclusions of different studies may vary slightly. Zuo *et al.* found at the order level, *Caudovirales* were the predominant phages while at the genus and species level, *Ascovirus* and *Streptococcus* phage were the dominant viruses through viral genome sequencing of the intestinal mucosa of UC patients.[32] They also observed decreased diversity, richness and evenness of *Caudovirales* phages in UC mucosa and more abundant *Escherichia* phage and *Enterobacteria* phage in UC mucosa. [32] They further demonstrated that UC is characterized by substantial alterations of the mucosa virobiota with functional distortion.[32] Jason *et al.* explored the changes in abundance of *Caudovirales* bacteriophages in IBD patients, they found that *Caudovirales* bacteriophages expand in IBD patients, especially in CD patients, [33] While non-significant results were reported in other research. [34] So far, researches on the enterovirus group have tended to reduce the diversity of gut bacteriophages and increase the abundance of *Caudovirales* in IBD patients, but no consensus has been reached, which may be related to small sample size, geography, treatment plan, mucosa or feces, lesion site, disease activity, *etc.*

IBD is correlated with intestinal microbiota imbalance, and the number of bacteriophages is correlated with the type and abundance of intestinal microbiota. Phages play an important role in the occurrence and development of IBD. For instance, Clooney *et al.* identified differences in the abundance of temperate bacteriophages between IBD and non IBD patients, and the number of temperate bacteriophage sequences in patients with CD increased. [34] In patients with active UC, higher proportions of temperate bacteriophages infected with *Bacteroides uniformis* and *Bacteroides thetaiotaomicmicon* were detected, both of which have been shown be beneficial for intestinal homeostasis. [35] Other research revealed that during colitis, the intestinal phage population was altered and transformed from an ordered state into a stochastic dysbiosis.[36] The data suggest a correlation between the host's inflammatory response and compositional changes in the intestinal phage communities.

### *Phages influence IBD through targeting microbiota and regulating immune*

Previous studies have found a negative correlation between the diversity and abundance of gut bacteria and changes in viral groups. [32,33] However, a small number of bacteria exhibit a positive correlation with bacteriophages, such as *Prevotellaceae*. There are differences between UC and CD patients, indicating disease specificity in the gut virus bacterial relationship in IBD patients.[33]

Evidence has suggested that viruses can affect the immune system of mammals. [37] Phage virus particles can transfer from the top of intestinal epithelial cells to the outer surface through transcytosis which makes it possible for these virus particles to directly contact the bottom immune cells of the intestine and stimulate various immune responses.[38] Fatemeh *et al.* induced

inflammatory response using dominant phages in the gut of IBD patients and found that these dominant phages can stimulate pro-inflammatory responses of macrophages to varying degrees affect the immune system. The production of interleukin (IL)-12 was significantly enhanced; However, increasing the number of nondominant phages weakened the pro-inflammatory effect of macrophages and increaseed the production of anti-inflammatory factors, thereby inhibiting the production of inflammation.[39] This demonstrates that bacteriophage regulate inflammatory bowel disease through immune modulation.

Phages also influence IBD by targeting microbiota. Research has shown that phages can target suppress *Klebsiella pneumoniae* (Kp), which can induce intestinal inflammation in mice, thereby, alleviating intestinal inflammation.[40] A cross infection experiment with microorganisms in the body found fecal virus like particles (VLP) originating from UC patients can specifically altering the relative abundance of several bacterial communities associated with the progression of IBD, thereby exacerbating dextran sulfate sodium salt (DSS) induced colitis.[41] Therefore, bacteriophages are dynamic modulators of the bacterial community in the intestine, playing a significant role in regulating intestinal inflammation and diseases.

At present, there is no consensus on the relationship between the differences in viral groups between IBD and healthy individuals and the pathogenesis of IBD patients. The reasons for changes in the abundance and diversity of intestinal bacteriophages are still unclear and may be related to intestinal bacteria. Phages may further participate in the pathogenesis of IBD by influencing the microbiota, and may themselves have a certain impact on the pathogenesis of IBD. This requires more research on the involvement of bacteriophages in the pathogenesis to confirm.

### *Phage and mammalian immunity*

Adiliaghdam *et al.* evaluated the immune regulatory effect of the virus by isolating it from patient colon surgical tissue and transmitting it to human macrophages and intestinal epithelial cells (IECs), and cultivating mice with humanized viruses *in vivo*. They found that the viral group from the colon tissue of IBD patients was interfered with, including a significant increase in eukaryotic enteroviruses and *coccidioviridae* phages, causing loss of phenotype of pro-inflammatory macrophages and intestinal epithelial cell (IEC) barriers after metastasis, and causing intestinal inflammation in the body.[42] Gogokhia *et al.* found that enhanced bacteriophages abundance exacerbates intestinal colitis through Toll-like receptor 9 (TLR9) and Interferon-g (IFN-g), not bacterium. They also observed expansion of $CD8^+$ T cells, indicating that phages may activate these cells. [43] These researches suggest that bacteriophages can directly activate mammalian immunity, bypassing bacterial hosts, and perhaps participate in the pathogenesis of IBD in this way.

## PHAGE THERAPY FOR IBD

In recent years, the use of antibiotics has led to the gradual emergence of bacterial resistance, including the emergence of super bacteria. To address this challenge, researchers have shifted their focus to bacteriophage therapy, which involves selectively killing bacteria using bacteriophages, thus controlling bacterial infections and regulating the gut microbiota.

Studies have demonstrated that bacteriophages can be used to treat patients with diabetes foot complicated with *Klebsiella pneumoniae* infection. [44] Lasha Gogokhia *et al.* established bacterial mouse models with *Bacteroides fragilis*, *Lactobacillus johnsonii*, *Bifidobacterium longum* and *Clostridium symbiosum* with *E. coli NC101*, and treated them with bacteriophages. They found that single delivery of bacteriophage mixtures reduced *E Coli NC101*, but subsequent bacteria rebounded and resistant occurred. However, continuous administration of phages was enough to continuously inhibit the bacterial growth in the tissue. By measuring the percentage of $CD4^+$and $CD8^+$T cells in mesentery lymph nodes (MLN) of phage-treated animals, they found that after phage treatment, the immune induction of experimental animals was upregulated, including innate and adaptive immunity.[43] This indicates that bacteriophages may control local inflammation in the intestine through immune responses. A child experiment in Bangladesh showed that multiple bacteriophages worked together, which was more effective than a single phage therapy in treating acute bacterial diarrhea in children.[45] This approach is known as "bacteriophage cocktail therapy", which refers to the combination of three or more bacteriophages to kill bacteria, especially super bacteria. This bacteriophage cocktail therapy can target and kill bacteria without increasing the resistance of other nondominant bacteria.[46] Van Belleghem *et al.* found that *Staphylococcus aureus* and *Pseudomonas aeruginosa* phages induced proinflammatory and anti-inflammatory responses of peripheral blood Monocyte.[47] They found that phages down regulated the expression of CD14, TLR4 (its activation induces the secretion of proinflammatory chemokines and cytokines) and Lysozyme, and up regulated the expression of IL-10. IL-10 has effective anti-inflammatory properties, indicating that phages may regulate intestinal inflammation in patients with IBD. Titécat Marie *et al.* showed that adhesive invasive *Escherichia coli* (AIEC) targeted phage therapy reduced AIEC in the gut of IBD mouse models and alleviated

intestinal inflammation in mice.[48]

Federici Sara *et al.* confirmed the feasibility of oral phage therapy to avoid bacterial resistance, targeting Klebsiella pneumoniae (Kp) to alleviate IBD.[40] By identifying the correlation between Kp and the severity of IBD, they found that Kp2 class strains effectively colonized and triggered immune responses in the colon. Subsequently, Kp2 strain isolated from IBD patients was colonized in sterile mice, and it was found that compared to non Kp2 strain colonized mice, Kp2 strain colonized mice showed higher levels of interferon-γ and lower IL-10 expression, indicating the pro-inflammatory effect of Kp2 strain. Afterwards, they continuously tested and selected bacteriophage cocktails targeting Kp2 bacteria-bacteriophage cocktails 5 (E),[40] which involved MCoc5c, 8M-7, 1.2–3 s, KP2–5–1 and PKP-55, and found that bacteriophage cocktails 5 (E) colonization significantly improved intestinal inflammation and tissue damage in DSS-induced colitis mice colonized with KP-2H7, while the control group treated with excipients showed severe inflammatory processes. This indicates that bacteriophage therapy can inhibit IBD related flora and treat intestinal diseases.[40] And through testing the survival rate of bacteriophages in artificial human gut systems, it was found that bacteriophages targeting the KP2 class of bacteria were stable in the human gastrointestinal tract, demonstrating the potential of bacteriophage therapy in the treatment of IBD. However, for subclinical inflammation, the effectiveness of bacteriophage therapy is not significant.

Phage therapy not only involves directly killing bacteria, but also targets the delivery of therapeutic drugs. [49] By cleaving specific bacteria, phages release the carried therapeutic drugs to the corresponding targets to achieve better therapeutic effects. Bacteriophages that naturally exist in the intestine possess better targeting, strong therapeutic effect, and minimal toxic side effects, being expected to become ideal drug delivery tools.

## FUTURE DIRECTIONS

IBD has emerged as a significant a global health concern, and various treatment options have been explored to address it. In addition to amino salicylic acid, glucocorticoid, immunosuppressant, fecal bacteria transplantation, biological agents, such as anti-tumor necrosis factor (TNF) antibodies, anti-integrin antibodies, anti-IL-12/23 antibodies, Janus kinase (JAK) inhibitors and S1P receptor regulators, among these, bacteriophages have also gained considerable attention in IBD research due to their ease of availability and efficiency. In addition to destroying bacteria directly, some gene products encoded by bacteriophages also have good bactericidal effects, which has become another promising development direction of bacteriophage therapy. In conclusion, while bacteriophages show great promise as a potential treatment for IBD, more research evidence is required to elucidate their precise mechanisms of action in bacterial and immune regulation. More prospective clinical studies are needed in the future to confirm the therapeutic effect of bacteriophages in IBD patients. Continued exploration and research efforts are needed to fully harness the potential of bacteriophages in IBD treatment.

## DECLARATION

### *Acknowledgement*
The authors acknowledge Dr. Shuang Chen (Cedars Sinai Medical Center) for revising and polishing this manuscript.

### *Author contributions*
All authors participated in the conception and design of the study. Xiaotong Shen researched the topics and drafted the manuscript. Airu Liu, Xiaonan Liang and Xiaolan Zhang reviewed and edited the manuscript. The authors read and approved the final manuscript.

### *Source of funding*
This work was supported by the National Natural Science Foundation of China (No. 82070563).

### *Ethical approval*
Not applicable.

### *Informed consent*
Not applicable.

### *Conflict of interest*
No potential conflict of interest was reported by the authors.

### *Data availability statement*
Not applicable.

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