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Gut virome and its implications in the pathogenesis and therapeutics of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) refers to chronic, recurrent inflammatory intestinal disorders, primarily including Crohn's disease (CD) and Ulcerative colitis (UC). Numerous studies have elucidated the importance of the gut microbiome in IBD. Recently, numerous studies have focused on the gut virome, an intriguing and enigmatic aspect of the gut microbiome. Alterations in the composition of phages, eukaryotic viruses, and human endogenous retroviruses that occur in IBD suggest potential involvement of the gut virome in IBD. Nevertheless, the mechanisms by which it maintains intestinal homeostasis and interacts with diseases are only beginning to be understood. Here, we thoroughly reviewed the composition of the gut virome in both healthy individuals and IBD patients, emphasizing the key viruses implicated in the onset and progression of IBD. Furthermore, the complex connections between the gut virome and the intestinal barrier, immunity, and gut microbiome were dissected to advance the interpretation of IBD pathogenesis. The updated discussion of the evidence regarding the gut virome will advance our knowledge in gut virome and chronic gastrointestinal diseases. Targeting the gut virome is a promising avenue for IBD treatment in future.

Keywords Gut virome-host interactions, Phage, Eukaryotic gut virome, Fecal virome transplantation, Crohn's disease (CD), Ulcerative colitis (UC), Inflammatory bowel disease (IBD)

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Background

Inflammatory bowel disease (IBD) is a chronic, recurrent condition posing a significant public health challenge [1]. Its diagnosis and management remain complex due to the largely unknown etiology, necessitating further exploration of disease mechanisms and precision therapies [2, 3]. IBD arises from genetic predispositions interacting with intestinal microbial imbalances, heightened immune responses, pro-inflammatory diets, and specific environmental factors that trigger harmful inflammation [4–9].

The rapid advancement in microbiome sequencing and analysis has intensified research on gut microbiota [10]. While significant progress has been made in understanding the bacterial components of the gut microbiome [11, 12], the gut virome has received less attention due to incomplete virome libraries and technological challenges [13, 14].

The gut virome, known as the "dark matter" of the gut microbiome, is a largely unexplored viral component within the human gastrointestinal tract. The human gut virome, predominantly composed of phages, can reach concentrations of 10^9 to 10^{10} viral particles per gram in feces, highlighting their abundance and persistence [15]. While these viruses generally do not cause significant clinical symptoms in humans, they may be essential for maintaining the ecological balance of intestinal microbiota. In recent years, researchers have established a series of human gut virome databases that have substantially enhanced our understanding of viral genomes, providing a wealth of annotated information. Prominent databases encompass the Gut Virome Database (GVD), Cenote Human Virome Database (CHVD), Metagenomic Gut Virus Database (MGV), and Gut Phage Database (GPD). Recent research underscores the vast genetic diversity and complex functional capabilities of the gut virome, indicating its significant impact on human health (Fig. 1A) [16].

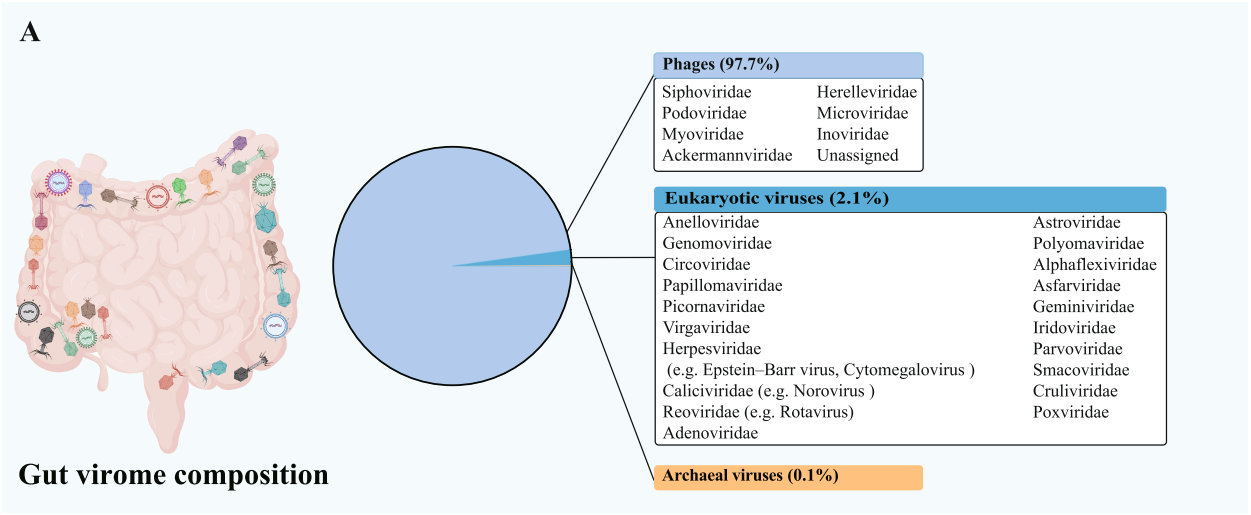
Research into the gut virome is nascent, yet numerous studies have linked its community structure disruption to IBD [23]. Notably, alterations in colonic viromes in IBD independently trigger intestinal inflammation in mice [24]. This connection between the gut virome and IBD has garnered significant attention. *Caudovirales* is an order of double-stranded DNA bacteriophages. The order includes three families: *Myoviridae*, *Siphoviridae*, and *Podoviridae*, distinguished by the structure of their tails. *Caudovirales* phages infect a wide range of bacterial hosts, playing a crucial role in shaping bacterial populations and influencing microbial ecology [25]. *Microviridae* is a family of small, single-stranded DNA bacteriophages that infect a variety of bacteria. The family includes several genera, with Microvirus being the most well-known. *Caudovirales* and *Microviridae* are both important members of gut phageome [26]. It has been reported that the abundance of *Caudovirales* and *Microviridae* changes during IBD [23, 27, 28]. Moreover, various eukaryotic viruses, especially those of the *Herpesviridae* family, have long been known to interact with IBD. Specifically, *Herpesviridae* was one of the most prominent viral families, making up ~ 12% of the total, second only to *Partitiviridae*, which was the most abundant across Ctrl, UC, colitic CD, and ileal CD patients [29]. The changes in enterovirus species associated with IBD have been partly clarified, but limited data reveal the mechanisms by which they influence diseases [17]. More profound insights into the mysterious nature of the enteric virome will provide new research directions (Fig. 1B).

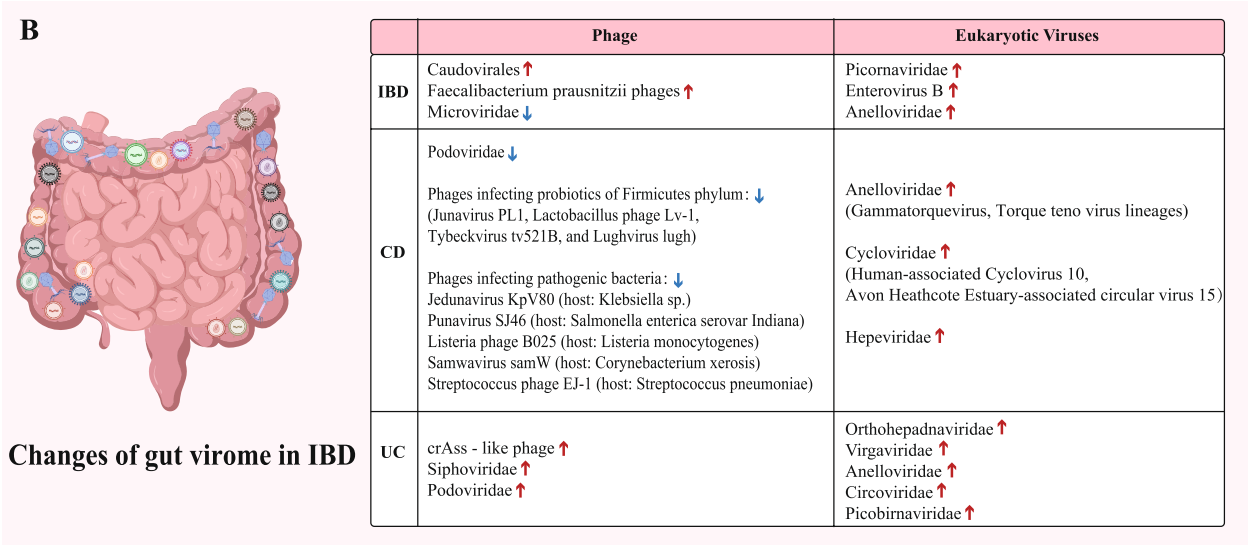
Here, we aimed to broadly collate recent research on the enteric virome and elucidate its potential correlation with the occurrence of IBD. Ultimately, more achievements will be made in the field of enteric virome studies, which will aid in elucidating the viral etiology of IBD to guide the potential clinical translation of virome-based diagnostic biomarkers and selectively targeted therapies.

Novel techniques for gut virome analysis

New techniques, including metaviromics, metagenomics, metatranscriptomic, metabolomics, metaproteomics, and next-generation sequencing (NGS), have revolutionized the study of gut viruses by enabling high-throughput, comprehensive analysis of viral communities [14, 18, 30]. These methods allow for the identification of a vast array of viruses, including many novel and previously uncharacterized strains, offering deeper insights into the virome's role in health and disease. Additionally, integrative multi-omics has emerged as a new trend in gut virome research. By integrating data on gut microbiota, virome, host gene expression, and metabolites, researchers can gain a more comprehensive understanding of how gut viruses influence host metabolic pathways and immune responses [31]. The ability to perform high-resolution virome profiling holds promise for more precise diagnostic tools and therapeutic strategies, paving the way for targeted interventions in IBD. Researches on novel techniques for gut virome analysis are underway.

Single-virus genomics (SVG) is a powerful tool for studying virus diversity and abundance in microbial environments. High-throughput SVG enables the discovery of nearly complete genomes of uncultured viruses, improving the coverage of viruses often missed in standard virome preparations. By combining next-generation short-read and long-read sequencing technologies, SVG allows for efficient virome analysis from clinical or environmental samples. It directly identifies and characterizes





	Phage	Eukaryotic Viruses
IBD	Caudovirales ↑ Faecalibacterium prausnitzii phages ↑ Microviridae ↓	Picornaviridae ↑ Enterovirus B ↑ Anelloviridae ↑
CD	Podoviridae ↓ Phages infecting probiotics of Firmicutes phylum: ↓ (Junavirus PL1, Lactobacillus phage Lv-1, Tybeckvirus tv521B, and Lughvirus lugh) Phages infecting pathogenic bacteria: ↓ Jedunavirus KpV80 (host: Klebsiella sp.) Punavirus SJ46 (host: Salmonella enterica serovar Indiana) Listeria phage B025 (host: Listeria monocytogenes) Samwavirus samW (host: Corynebacterium xerosis) Streptococcus phage EJ-1 (host: Streptococcus pneumoniae)	 Anelloviridae ↑ (Gammatorquevirus, Torque teno virus lineages) Cycloviridae ↑ (Human-associated Cyclovirus 10, Avon Heathcote Estuary-associated circular virus 15) Hepeviridae ↑
UC	crAss - like phage ↑ Siphoviridae ↑ Podoviridae ↑	Orthohepadnaviridae ↑ Virgaviridae ↑ Anelloviridae ↑ Circoviridae ↑ Picobirnaviridae ↑

↑ **Red upward arrow: An increase in number** ↓ **Blue downward arrow: A reduction in number**

Fig. 1 **A** Composition of gut virome in health: phages (*Siphoviridae*, *Herelleviridae*, *Podoviridae*, *Microviridae*, *Myoviridae*, *Inoviridae*, *Ackermannviridae* and unassigned), Eukaryotic viruses (*Anelloviridae*, *Astroviridae*, *Genomoviridae*, *Polyomaviridae*, *Circoviridae*, *Alphaflexiviridae*, *Papillomaviridae*, *Asfarviridae*, *Picornaviridae*, *Geminiviridae*, *Virgaviridae*, *Iridoviridae*, *Herpesviridae*, *Parvoviridae*, *Caliciviridae*, *Cruliviridae*, *Reoviridae*, *Poxviridae*, *Adenoviridae*), Archaeal viruses. (based on the GVD database). **B** Changes of gut virome in IBD: IBD (*Caudovirales*, *Faecalibacterium prausnitzii* phages, *Picornaviridae*, *Enterovirus* B and *Anelloviridae* increase, while *Microviridae* decrease), CD (*Anelloviridae*, *Cycloviridae* and *Hepeviridae* increase, while *Podoviridae*, phages infecting probiotics of *Firmicutes* phylum and phages infecting pathogenic bacteria decrease), UC (crAss-like phage, *Siphoviridae*, *Podoviridae*, *Orthohepadnaviridae*, *Virgaviridae*, *Anelloviridae*, *Circoviridae*, and *Picobirnaviridae* increase) [17–22]

viruses in complex microbial communities, offering insights into low-abundance or uncultured viruses that traditional methods often overlook [32]. Besides, SVG can analyze host-phage interactions, helping identify specific bacteriophages linked to IBD-related bacteria. This powerful framework holds potential for developing phage cocktails targeting these bacteria, offering a novel therapeutic strategy for IBD management [33].

Spatial transcriptomics is an emerging technology that combines traditional gene expression analysis with spatial information, allowing for the examination of gene expression patterns while preserving the spatial context of tissues [34]. The technique enables the creation of detailed spatial transcriptomic maps, revealing how gene expression is spatially distributed across different regions of the gut [35]. Therefore, this approach has transformative potential for understanding the complex gene regulatory networks in the gut, as well as for investigating how environmental factors, such as

microbiota composition and inflammation, influence gene expression in distinct gut regions.

Recent advancements in artificial intelligence (AI) and machine learning (ML) algorithms have revolutionized the analysis of large-scale virome data. A study analyzed 1282 fecal metagenomes from published studies, constructing a gut viral catalog using a reference-independent approach. Viral signatures were identified, and predictive models based on machine learning algorithms were developed, which showed the predictive power of gut viral biomarkers for non-invasive colorectal cancer and adenoma diagnostics [36]. As AI and ML techniques continue to evolve, their application in virome research promises to enhance our understanding of viral ecology, disease mechanisms, and potential treatments.

The gut virome community in healthy individuals

The intra-individual variations and inter-individual differences of gut virome

The gut microbiome is generally characterized by a teeming bacterial ecosystem. However, other symbiotic microorganisms in the gut, such as viruses, have also attracted attention. Overall, the human gut virome is a community including viruses that infect eukaryotic and prokaryotic cells. Recently, researchers have made considerable strides in the field of gut virome. Using different specimens, innovative methodologies for viral isolation and detection can gradually demystify the composition of the gut virome. In healthy adults, the gut virome generally comprises phages, eukaryotic viruses, and human endogenous retroviruses. Approximately 90% of the gut's 10^{15} viruses are part of the phageome, which affects various chronic diseases [37]. In comparison, eukaryotic viruses, though less prevalent, have been widely researched concerning intestinal diseases. Most of these studies focused on opportunistic pathogenicity. Another rare virus family, human endogenous retroviruses, is part of the human genome and influences diseases by modulating gene expression and immunity [38]. As special components, they may significantly contribute to antigens that induce aberrant immune responses in various diseases.

The composition of the gut virome is inherently variable and unstable throughout life. Previous research indicates its development is influenced by factors such as birth mode, feeding method, and delivery location [39, 40]. In healthy newborns, gut viruses are initially absent but appear soon after birth [41]. However, the viral diversity in a healthy infant is minimal during the first week, with little correlation to the mother's virome. Most of the identified sequences belong to the phageome and are correlated with the co-occurring bacterial community. Microarray analyses have highlighted the dynamic nature of the gut virome in infants during their first and second weeks [42].

A recent longitudinal study by William et al. examined the fecal virome of infants [43], revealing that it predominantly consists of phages and human host viruses, distinct from the maternal gut virome. Metagenomic sequencing suggests that prophages may initially colonize the gut within the first month after birth, while eukaryotic viruses become dominant around four months of age [41]. Phage diversity and abundance increase in the early weeks post-birth, peaking before gradually decreasing [42, 44]. Over the first two years, the eukaryotic virome expands, while the personalized phage composition contracts [44]. However, phages remain the predominant viruses in the adult gut.

During infancy, viruses that colonize the gut are mainly members of the *Siphoviridae* family (belonging to *Caudovirales*) [40, 45]. The early presence of the *Lactococcus* phage (*Siphoviridae* family) seemed to drive the development of the phage community [43]. As children grow, the diversity of gut viruses increases, and the phageome shifts to include a greater proportion of the *Microviridae* family [43]. Recent studies suggest that while *Caudovirales* dominate the gut virome in early life, *Microviridae* reach peak levels at approximately two and a half years old. By adulthood, the phageome is predominantly composed of *Caudovirales* [44, 46, 47].

Eukaryotic viruses, another important group in the gut virome, expand with age and are influenced by environmental factors, gradually becoming more similar to the mother's virome [43, 48]. Eukaryotic viruses, including circoviruses, parechoviruses, and even pathogenic viruses, such as rotaviruses, are frequently found in infants. In the initial months post-birth, RNA and DNA viruses from at least 16 families, such as anelloviruses, picornaviruses, caliciviruses, parvoviruses, adenoviruses, astroviruses, circuloviruses, polyomaviruses, and papillomaviruses, are actively involved [41, 42, 49]. The colonization and variation of eukaryotic viruses are complex, shaped by environmental factors [50].

In humans, the interpersonal diversity of viral families tends to be high, whereas the intrapersonal gut virome remains relatively stable over time [45, 51]. One study reported that infant monozygotic twins shared a more similar virome dominated by temperate phages than unrelated populations [52]. In a study by Hoyles et al., a unique virome assemblage was identified in each individual via pulsed-field gel electrophoresis [15]. Genetic background may play a key role in shaping these differences. In adult twins, the gut virome was observed to differ, possibly because of dynamic changes in microbiome diversity.

The gut virome's dynamics are enigmatic, with numerous unknowns in this field. To enhance comprehension of viruses in disease, it is essential to identify distinct gut viromes at various life stages and examine factors influencing individual differences in gut viromes.

Gut phageome

Hoyles et al. reported that the number of virus-like particles (VLPs) contained in the fecal filtrate was up to 10^{12} VLPs per gram of sample using epifluorescence microscopy, while transmission electron microscopy highlighted the diversity of gut VLPs, identifying bacteriophages as the predominant species. The abundance of the gut virome suggests a potential critical roles [15].

Because many unassigned sequences have not been mapped to viral libraries, the categories of viruses that comprise the core gut virome have not been confirmed. The phageome is the most important member of the gut virome family. Analysis of the gut virome shows that *Caudovirale* and *Microviridae* families dominate the intestinal mucosal surface in healthy individuals [45, 51, 53]. Bacteriophages in the human gut are typically classified into *Siphoviridae*, *Myoviridae*, and *Podoviridae* families, with the crAssphage, a member of *Podoviridae*, likely infecting Bacteroides [54–56]. Additionally, new virus families in the gut are being identified. Recent discoveries in Tanzania and the Laksam region have identified Lak phages with notably large genomes, yet their characteristics remain largely unexplored [57]. These phages, as symbiotic modulators, play a crucial role in sustaining intestinal homeostasis by engaging in complex interactions with the immune system and other microbiome components [58–60].

Eukaryotic gut virome

In addition to phage species in the gut, some eukaryotic viruses are classified as commensal organisms that exhibit critical functions, particularly in the absence of disease. Studies of the gut virome have identified at least 16 viral DNA families and 10 RNA families in gut samples [61]. Transient chronic infections can involve 50–100 viral species [62]. In experiments, mice pretreated with antivirals exhibited more severe dextran sulfate sodium(DSS)-induced colitis, similar to IBD pathologies [63]. These results highlight the necessity of certain eukaryotic viruses in the gut microecosystem, including pathogenic families regulated by intestinal defenses.

Throughout their life course, rather than remaining a static community, eukaryotic gut viruses undergo continuous alterations. In summary, no one has an identical and stable composition of the gut eukaryotic virome. Furthermore, evidence defining the viral families present during different life stages, irrespective of healthy or diseased states, has not been clearly presented. Decoding critical members of the gut virome and dissecting their roles may offer new insights into the onset and alternative therapeutics for intestinal diseases.

Human endogenous retroviruses (HERVs)

Human endogenous retroviruses (HERVs), comprising 8% of the human genome, originate from retroviral infections of germ line cells [64]. These DNA sequences, integrated into the genome, were historically regarded as non-functional. The majority of sequences lack replication capability and do not encode proteins [65]. HERVs are classified into three main classes—class I (Gammaretrovirus and Epsilonretrovirus genera), class II (Betaretrovirus genus), and class III (Spumaretrovirus genus)—based on the sequence similarity of their polymerase genes [66]. Additionally, the distribution of sequences across various loci within the human genome varies among the different HERV groups [67]. The regulation of HERVs involves both control and reactivation mechanisms. Typically, HERVs may remain silent due to mutations and be under epigenetic control. However, environmental factors can modify these epigenetic controls, reactivating HERV expression. Such factors include exogenous viruses, infectious pathogens, aging-related processes, radiation, epigenetic drugs, mitogens, or cytokines, which can, in turn, affect the host's vital physiological functions [68]. Recently, several studies have indicated that HERVs act as gene expression regulators in developmental processes, immune regulation, cancer, autoimmune diseases, and neurological disorders [38]. Typically silenced, HERVs can be activated in response to infection, trauma, or other disease states.

The gut virome community in IBD

Gut phageome and IBD

In an earlier study, researchers found an elevated number of gut VLPs in CD [23]. Unfortunately, the current virus library does not allow for the annotation of certain particles. Several studies focusing on virome alterations in IBD have made clearer discoveries later [28, 30, 69, 70]. A general trend is that bacteriophage families targeting beneficial bacteria increase the inflammatory status of IBD. Research indicates that in IBD patients, *Caudovirales* levels rise while their diversity declines, suggesting that phageome dysbiosis contributes to intestinal inflammation [23, 27, 28, 71–74]. Furthermore, these patients show reduced richness and relative abundance of *Microviridae*. This is accompanied by an increase in harmful bacteria and a decrease in beneficial bacterial species [23, 75]. In contrast, our study found a higher abundance of *Microviridae* in the gut mucosal virome of UC patients compared to healthy controls [27]. The heterogeneity in

research results is attributed to variations in sample categories. In patients with CD, the gut phageome structure and virus-bacteria interactions differed from healthy controls, with some cohort-specific variations [19]. Discrepancies in study conclusions may arise from differences in disease states, sample types, and sequencing methods.

The phageome in patients shifted from a virulent (lytic) to a temperate (lysogenic) life cycle, resulting in bacteriophage genes coexisting in equilibrium with the host [73]. Recent data revealed that gut metabolic functions are encoded by bacteriophage genes [76]. Disorders in these functions may predispose individuals to autoimmune diseases, highlighting the pathogenicity of lysogenic conversion. Simultaneously, this reminds us to explore the functional and metabolic changes that occur in the gut phageome in IBD rather than investigate the quantity of phages. A recent study focused on the ileal virome of CD [19]. Both virulent and temperate bacteriophages decreased in the ileal mucosa. However, its association with CD onset remains unclear. In humans, the gut phageome can maintain homeostasis only if the phages involved are present in the appropriate composition and concentration. Characteristic changes that occur in the gut phageome during IBD may serve as new biomarkers and therapeutic targets.

Eukaryotic gut virome and IBD

During IBD, eukaryotic viruses undergo complex changes. Multiple independent studies have emerged, raising various concerns. For instance, in a cross-sectional study, human adenoviruses were predominant in individuals with IBD; however, no direct causation was confirmed between the viruses and IBD [77]. Altered levels of gut viruses offer clues to their pathogenicity in IBD. Metagenomic analysis of the gut virome in early-diagnosed patients showed increased *Hepadnaviridae* levels in UC and elevated *Hepeviridae* in CD, while UC exhibited reduced *Polydnaviridae* and *Tymoviridae*, and CD showed decreased *Virgaviridae* [29]. Another study found increased *Pneumoviridae* and decreased *Anelloviridae* in UC, suggesting specific virome dysbiosis in CD may aid diagnosis [27]. A prior study indicated an increase in DNA eukaryotic Torque teno virus and RNA tomato diet-related virus in CD [75]. A recent cross-sectional study involving 577 IBD flare patients and 8826 unmatched controls found a higher norovirus positivity rate in CD patients [78]. However, individual gut virome variability and confounding factors complicate these results.

The *Herpesviridae* family, encompassing cytomegalovirus (CMV) and Epstein–Barr virus (EBV), is actively researched in the context of IBD. The detection modalities used in these studies have been comparably reliable. Members of this virus family, which exhibit physiological hepatic tropism, have been found to be more distributed in the intestinal lumen of patients with IBD than in controls [29, 77]. CMV is considered a causative factor for colitis in vulnerable individuals. It can remain latent in healthy asymptomatic individuals but can later be reactivated upon immunosuppression in IBD and replicate more actively in these patients [79, 80]. Intriguingly, researchers have not observed any obvious effects of antiviral treatment on the outcomes of CMV-positive IBD patients [81–83]. Thus far, most studies have indicated that CMV acts as an innocent bystander and not as a viral trigger for IBD.

EBV infection is often seen in patients with IBD [84]. Mechanisms of EBV-aggravated colitis have been elucidated in recent studies [85]. Further, the roles of EBV in triggering IBD have evoked worldwide interest. Research has confirmed the significant presence of EBV DNA, EBV-positive lymphocytes, EBV-encoded mRNA, and EBI3 in inflamed colonic mucosa [86]. Quantitative variations in plasma EBV DNA load between individuals with and without IBD suggest EBV's potential role as a risk factor in IBD pathogenesis. Furthermore, the role of EBV in predisposing individuals to IBD has been reported. A study demonstrated that individuals with a history of EBV infection are more likely to develop IBD, highlighting EBV's functional diversity in the gut [87]. Studies exploring the direct causal link between EBV and inflammatory bowel disease (IBD) show promise. In summary, the enteropathogenic properties of members of the *Herpesviridae* family as triggers of inflammation require comprehensive exploration.

Orthohepadnavirus, a genus within the *Hepadnaviridae* family, encodes the hepatitis B virus X protein (HBx). One study found that pediatric patients with UC had elevated HBx levels [29]. Based on this, cutting-edge research has identified this virome-derived factor as directly involved in UC pathogenesis [88]. The researchers confirmed elevated HBx transcript levels in the colonic biopsies of patients with HBx-positive UC. Furthermore, HBx binds to certain intergenic DNA regions, thereby disrupting intestinal physiology by impairing the epithelial barrier and affecting the gut immune system.

A disrupted intestinal microbiome is one of the most substantial contributors to IBD. We hypothesize that eukaryotic viruses, as essential elements of the gut microbiome, may change prior to or during the onset of IBD. To date, studies have successfully indicated alterations in eukaryotic viral families that occur in IBD. Despite these findings, related studies have been independent and have not provided comprehensive views on all eukaryotic viromes involved in IBD.

HERVs and IBD

The expression of HERVs in humans has received more attention in investigations of autoimmune diseases such as IBD. Studies have identified an increased presence of HERVs in Crohn's disease (CD) patients, potentially linked to immune regulation [70]. Research involving the intestinal tissue RNA virome of pediatric IBD patients has expanded the examination of HERVs [89]. A 2018 study thoroughly assessed HERV expression in ileal and colonic tissues from CD patients and healthy controls, revealing a tissue-dependent expression profile [90]. Specifically, HERV-Wenv and HERV-FRD-env expressions were downregulated in inflamed tissues of CD patients. The diminished expression of these HERVs leads to a deficiency in the HERV-derived protein syncytin, which damages the immunosuppressive activity in normal intestinal tissue. A metagenomic analysis of colon tissue from IBD patients revealed a significantly higher abundance of HERV-K and HERV-H reads compared to HERV-W. The IBD libraries, *cdC08* and *ucC07*, exhibited significantly higher relative abundance and diversity of HERVs and viral strains compared to other samples. Additionally, the abundance of HERVs in libraries containing herpesviruses was 5 to 10 times higher than in those without. Infection with certain viral strains, like *Herpesviridae*, may trigger HERV expression in the colon [69]. Similarly, external viral infections can activate HERV expression, potentially leading to cytotoxic structural protein expression [91, 92]. Additionally, a study reported significantly elevated transcriptional levels of HERV-H-pol ($p=0.0003$) and HERV-K-pol ($p=0.001$) in individuals with IBD compared to healthy controls. TRIM28 transcript levels, associated with epigenetic regulation and immune modulation, were significantly reduced in IBD patients ($p<0.001$) [93]. These findings provide insights into IBD pathophysiology. However, The specific roles of HERVs in the disease process of IBD patients are yet to be determined, necessitating further studies for confirmation.

The gut virome's potential implications on gut homeostasis

Gut virome and intestinal barrier

The breakdown of the intestinal barrier is a crucial factor in the development of IBD. Our findings suggest that the gut virome plays a vital role in maintaining epithelial barrier integrity, indirectly influencing IBD pathogenesis. A protective barrier consisting of various bacteria and extracellular matrix exists within the lumen. Some phages have been shown to encode depolymerases that degrade the extracellular matrix, whereas others have been reported to release and engage in forming biofilms [94, 95]. It is reported that some bacteriophages act as a biological barrier by binding their Hoc protein to MUC2 in the intestinal mucus and lead to increased intestinal mucus production, preventing bacterial invasion, such as *E. coli* phage, øPNJ-6 [96]. These findings suggest that the phageome has opposing effects on the regulation of the intestinal barrier, probably because of different phage species (Fig. 2A).

The murine norovirus (MNV), often classified as a conditional pathogen, does not promote inflammatory pathologies. In cooperation with other genetic factors, MNV induces intestinal inflammatory abnormalities in mice. Recent experimental evidence suggests that MNV infection and mutations in the IBD susceptibility gene Atg16L1 act in concert to induce inflammatory gastrointestinal pathologies in response to DSS, which resemble the intestinal inflammation observed in patients with CD [97]. The authors further validated that the existence of MNV promoted intestinal abnormalities in IBD models with Atg16L1 mutations but restored intestinal morphology in antibiotic-treated mice by imitating the functions of intestinal bacterium [97]. The data from Cadwell et al. revealed that the elimination of MNV eliminated this inappropriate response. MNV infection and Atg16L1 mutations increase susceptibility to intestinal inflammation. These individuals show reduced viability and functionality of Paneth and other intestinal epithelial cells. MNV infection disrupts lysozyme exocytosis and mucus secretion by goblet cells, compromising the intestinal barrier and supporting the multi-hit model of IBD pathogenesis, thereby promoting colitis [98, 99]. Similarly, in interleukin (IL)−10-deficient mice, MNV could injure the epithelial barrier and subsequently promote intestinal inflammation [100]. Surprisingly, MNV can provide partial or complete beneficial functions that mimic those of commensal bacteria. One study reported that MNV can restore intestinal morphology and support immune balance [101]. Altered small intestinal morphology, Paneth cell defects, and damaged local immune systems have been found to be reversed by MNV. The findings suggest a potential protective role of MNV in maintaining the intestinal barrier.

Other enteric viruses, such as CMV, can enhance epithelial turnover and repair through interferon (IFN)-I signaling [102]. In addition, viral signaling can influence gut epithelial permeability. When administered with a preparation that mimics viral double-stranded RNA, experimental rats displayed reduced colonic epithelial permeability but increased epithelial permeability in the ileum ex vivo [103]. Taken together, these findings demonstrate the complex effects of the enteric virome on the intestinal barrier, which may be beneficial or pathogenic. Achieving equilibrium in the variety and functions of countless gut viruses is worth investigating. More

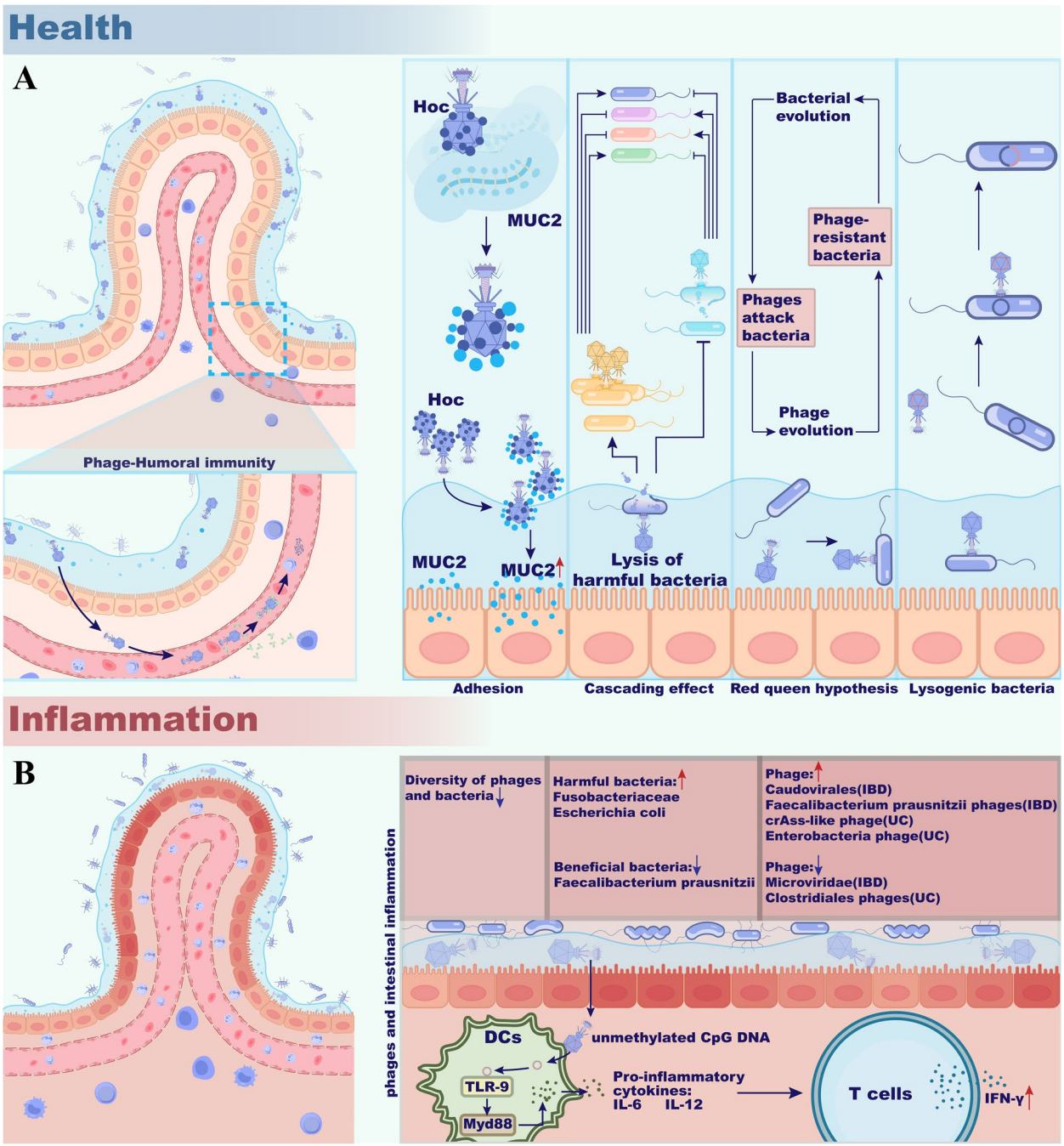


Fig. 2 Relationship between gut phages and intestinal health and inflammation. **A** Mechanisms by which phages defend against bacterial invasion and maintain gut homeostasis in health. (1) Adherision: phages form a biological barrier by binding Hoc protein to MUC2 in intestinal mucus, enhancing mucus production and preventing bacterial invasion. (2) Cascading effect: phages lyse pathogenic bacteria, releasing metabolites and progeny phages, thereby influencing the survival dynamics of neighboring bacterial species. (3) Red Queen hypothesis: phages and bacteria co-evolve, with phages selectively lysing specific bacterial strains while adapted phages survive and propagate. (4) Lysogenic bacteria: some phages integrate their genome into bacterial hosts, forming lysogenic bacteria; under stable conditions, this state persists, but external triggers may induce bacterial lysis. (5) Phage-humoral immunity: phages penetrate the gut lamina propria and enter circulation, activating innate and adaptive immunity; B cells differentiate into plasma cells, generating antibodies that neutralize phages, maintaining gut homeostasis. **B** Mechanisms by which phages contribute to gut inflammation. (1) Changes in the number and diversity of phages and bacteria during intestinal inflammation. (2) Phages activate dendritic cells, initiating T cell–mediated inflammation

evidence from patients with IBD is needed to confirm these laboratory conclusions (Fig. 3).

Gut virome and host immune system

The enteric virome is the key regulator of the intestinal immune system. Certain viruses, such as herpesviruses and polyomaviruses, are known to induce persistent low-level immune responses without noticeable symptoms, acting as commensal agents to modulate intestinal immunity [59]. Similarly, enteric phages can influence immune regulation and overall health akin to eukaryotic viruses [104]. The bacteriophage adherence to mucus model suggests that immunoglobulin-like protein domains on phage capsids could provide non-host-derived innate immunity, aiding phage integration into gastrointestinal mucosa to combat bacterial infections [105, 106]. Studies indicate that orally administered phages trigger both innate and adaptive immune responses in hosts. Immune cells such as monocytes, dendritic cells, CD4 + T cells, and CD8 + T cells interact with the phageome, influencing the host immune

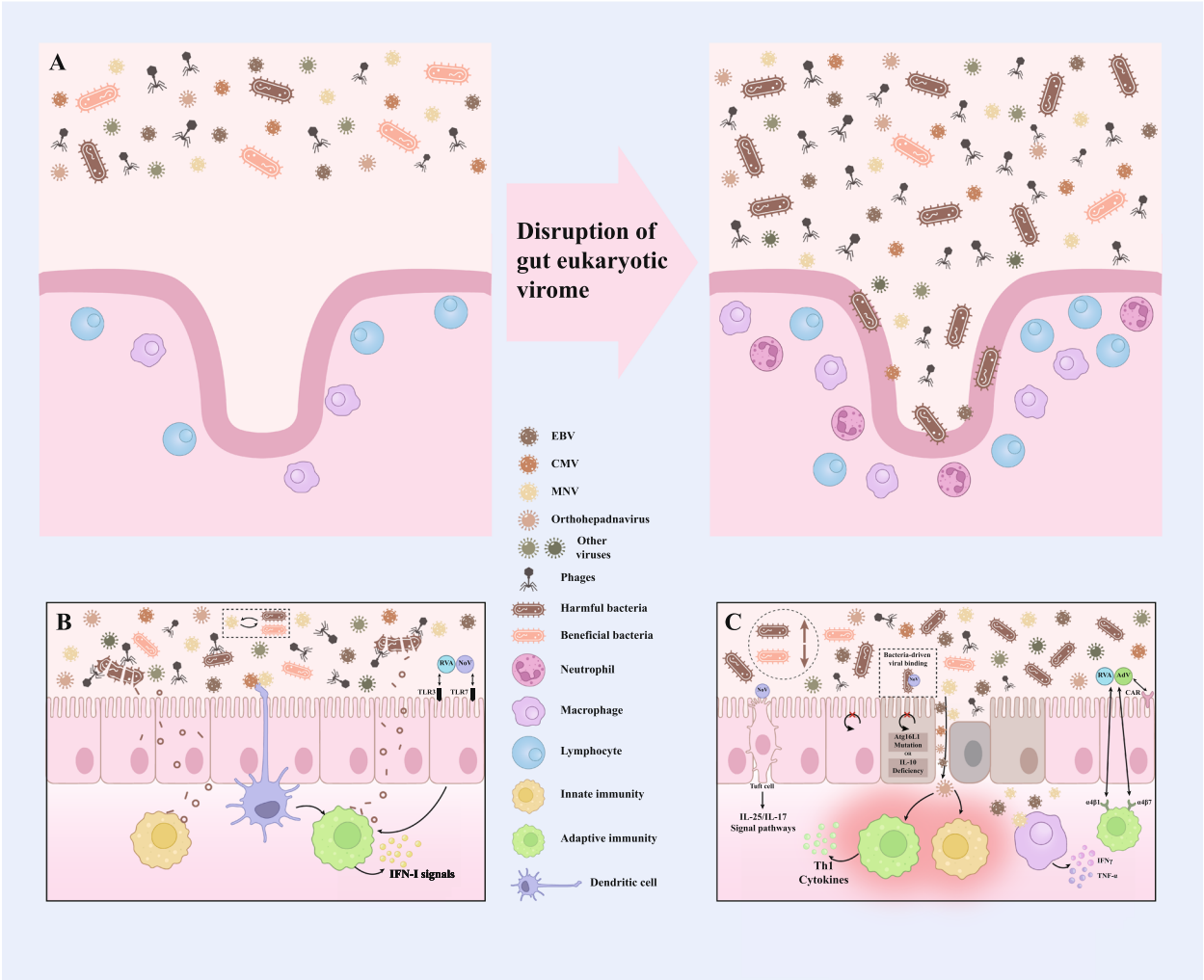


Fig. 3 Disruption of gut eukaryotic virome. **A** The disruption of gut eukaryotic virome influences gut homeostasis and leads to gut inflammation. **B** Balanced gut eukaryotic virome maintains the gut homeostasis. MNV can interact with bacteriome to act in intestinal microecology. CMV and MNV are proved to stimulate IFN-I signals to promote anti-inflammatory response, intestinal morphology, and function. RVA and NoV can also evoke protective adaptive immune response through TLR3 and TLR7. **C** Impaired gut eukaryotic virome triggered inflammation. Firstly, NoV is associated with IL-25/L-17 signal pathways, and it can increase the secretion of inflammatory cytokines relying on the virus entry in macrophages. Secondly, based on Atg16L1 mutation or IL-10, MNV can disrupt epithelial permeability, bacteriome and aggravate inflammation, with the binding to epithelium driven by bacteria. Thirdly, HBx possessed by Orthohepadnavirus play a role in the damage of the epithelial barrier and affect the gut immune system. Additionally, interaction of rotavirus and adenovirus with integrins, or activation of the CAR may participate in the pathogenesis of IBD. Finally, once the intestinal barrier is damaged, "bystanders" such as CMV further induce immune abnormality and pathologies

system [107, 108]. This suggests that gut phages play a role in shaping gastrointestinal immunity.

Phages in the gut influence host health and disease pathogenesis by directly interacting with the host or by modulating immune molecules [109]. The gut phageome plays a crucial role in sustaining anti-inflammatory responses and immune homeostasis. When phages penetrate the gut lamina propria and enter the bloodstream, they trigger innate and adaptive immune responses. B cells differentiate into plasma cells, producing specific antibodies that neutralize incoming phages, thus preserving intestinal homeostasis [110]. Enteric viromes downregulate inflammatory signals. Upon activation by viral RNA, dendritic cells release the anti-inflammatory IFN-β through Toll-like receptors 3 and 7 [63]. Treatment with TLR3 and TLR7 agonists alleviates DSS-induced colitis in mice. Rotavirus (RVA) and norovirus (NoV) can trigger protective adaptive immune responses via TLR3 and TLR7 [63]. Additionally, the binding of single-stranded viral RNA to NOD2 is linked to the autophagy pathway, initiating IFN-I signal production to reduce inflammation [111]. Murine norovirus (MNV) has been shown to mitigate inflammatory conditions by promoting IFN-I production through autophagy pathways and interacting with the bacteriome to influence intestinal microecology [101, 112]. The gut virome's protective role in intestinal immunity and its intriguing connection to IBD pathogenesis have been noted.

Several studies have revealed that IBD mainly originates from immune disorders involving multiple inflammatory pathways. Eukaryotic viruses and phages are considered direct activators of intestinal inflammation, acting as antigens to stimulate inappropriate immune responses in chronic gastrointestinal diseases. Additionally, the virus-infected state of the host may evoke a persistent immune response in cells, consequently predisposing individuals to develop intestinal inflammation [101]. Phages penetrate the lamina propria via transcellular phagocytosis and interact with dendritic cells (DCs). Unmethylated CpG DNA in phage genomes binds to the intracellular receptor TLR9 in DCs, triggering the activation of the downstream signaling molecule MYD88. This triggers the release of pro-inflammatory cytokines like IL-12 and IL-6, subsequently activating T cells. Activated T cells release significant levels of interferon-γ (IFN-γ), intensifying intestinal inflammation [109]. In ulcerative colitis (UC) pathogenesis, the HBx-induced immune alteration, characterized by reduced dendritic cells (DCs), CD8 + T cells, and neutrophils, compromises gut immune defense [88]. A study on noroviruses demonstrated that the virus specifically modifies intestinal immunity by influencing the autophagy signaling pathway, leading to the release of inflammatory mediators [101].

Noroviruses may exacerbate intestinal inflammation by increasing Th1 lymphocytic cytokine secretion, potentially through macrophage entry [113, 114]. Th1 cytokine blockers, particularly tumor necrosis factor(TNF)-α antagonists, are commonly used in IBD treatment [115]. In MNV-infected mice, TNF-α or IFN-γ antibody treatment alleviated intestinal inflammation [97, 115]. Recent studies suggest norovirus binding to tuft cells may influence the IL-25/IL-17 pathway in IBD [116, 117]. Rotavirus infections also elevate pro-inflammatory cytokines, worsening gut inflammation from epithelial damage [118]. Additionally, interactions of rotavirus and adenovirus with integrins or activation of the Coxsackie–Adenovirus Receptor (CAR) may contribute to IBD pathogenesis [119–121]. These immune responses to gut viruses could be involved in IBD onset.

A compelling recently explored topic involves neurogenic inflammation in IBD, which is attributed to the dysfunction of the epithelial cell–cell junctions and the neurogenic barrier in the gut [122]. Neuroinflammatory factor levels decline to a better level when a wide-spectrum antiviral agent is used, indicating the possible harmful effects of neuroinflammation associated with viruses in IBD [122]. Additionally, pathways with uncertain roles for the gut virome in IBD are worthy of further scientific investigation. Determining how to re-establish a balanced immune milieu through the enteric virome is promising for clinical application in the treatment of IBD (Figs. 2 and 3).

Interaction between gut virome and bacteriome

Viruses are not the sole microbes in the gut, and changes in their diversity and quantity are linked to shifts in bacterial groups, having more complex effects than previously understood [123, 124]. A pioneering study reported the increased presence of *Clostridiales*, *Alteromonadales*, *Clostridium acetobutylicum*-infecting phages, and *Retroviridae* family members, which fluctuate alongside bacteria in IBD patients, underscoring the need to strengthen research on correlation networks between bacteria and viruses [72].

Microbiome-to-microbiome interactions, such as possible crosstalk between the enteric virome, bacteriome, and mycobiome, have long been considered to impact intestinal homeostasis [125]. Phages lyse harmful bacteria, releasing metabolites and progeny phages that influence neighboring bacteria. These cascading effects can either benefit or harm the survival of other bacterial species. This study highlights the ecological role of phages in regulating bacterial balance and proposes their therapeutic potential in modulating the gut microbiome to maintain homeostasis [124]. In line with the Red Queen hypothesis, it suggests that phages and bacteria undergo

co-evolution. Phages selectively kill specific bacterial species, while those that survive continue to reproduce. Phages that cannot infect the surviving bacteria eventually die out, whereas those that adapt to new bacterial hosts continue to propagate [126]. However, some phages do not lyse bacteria but instead inject their genetic material, integrating it into the bacterial genome, creating lysogenic bacteria. Typically stable, this state can be disrupted by external stimuli, causing lysis, bacterial destruction, and gut inflammation [17]. This highlights how interactions between the virome and the gut bacteriome may affect IBD onset.

Zuo et al. have identified relationships between the virome and bacterial microbiome associated with IBD [27]. They compared the microbiome in the mucosa of UC patients with that of healthy controls. UC mucosa showed increased bacterial diversity and richness, with significant differences in microbial structure at the phylum, family, and genus levels. Additionally, there were significant changes in the relationship between the bacteriome and virome. In healthy controls, bacterial and viral diversity metrics correlated strongly, but these correlations were lost in UC. UC also exhibited more complex bacterial-viral interactions, with an increased number of correlations, though most were negative. Specifically, the correlations between certain bacteriophages and mucosal bacteria were weakened in UC. The altered virobiota-bacterial microbiota relationship in UC suggests a disruption in the balance between viruses and bacteria. Similarly, another large-scale study highlighted reduced viral-bacterial correlations in UC patients compared to healthy individuals [23]. In CD patients' ileum, mutualistic interactions involving *Bifidobacterium*, *Lachnospiraceae*, and bacteriophages were found to be lacking [19]. These findings underscore the significance of viral-bacterial interactions (Fig. 2).

Certain diseases, including IBD, are linked to specific bacterial genus dynamics that have been deciphered but not fully dissected. In murine models of norovirus infection, the inflammatory pathologies induced by MNV are highly dependent on gut microbiota [127]. The binding of norovirus to intestinal mucosa is mediated by bacteria. Supporting this finding, some beneficial effects of symbiotic bacteria that act in IBD progression have been found to be inhibited in murine models of norovirus infection. Besides, noroviral infections in humans could lead to decreased *Bacteroidetes* and increased Proteobacteria, both implicated in IBD pathogenesis, though further evidence is required [128]. These findings suggest that interactions between norovirus and gut bacteriome could be linked to IBD pathogenesis.

Bacteriophages are known microbiome regulators. Italian researchers discovered that phages from UC patients exacerbated DSS colitis by affecting the bacteriome [129]. Another study showed that increased temperate phages reduced anti-inflammatory gut symbionts like *Faecalibacterium prausnitzii*, contributing to IBD [130]. On the one hand, bacteriophages can induce bacterial lysis, releasing inflammation activators and triggering abnormal immune responses [23, 131]. On the other hand, integration of viral genetic material into the bacterial genome can lead to modifications in the bacterial metabolism, such as the alteration of nutrient utilization and energy production, ultimately impacting the microbial community's overall metabolic balance. Additionally, phages can facilitate the evolution of bacterial resistance mechanisms, such as the acquisition of virulence factors or antibiotic resistance genes, through processes like transduction. This can result in the emergence of bacterial strains that are more adept at surviving in the inflamed gut environment [132, 133]. In general, the phageome influences bacterial diversity, evolution, and metabolism to modulate their behaviors in IBD. Surprisingly, phages might also offer protection against chronic intestinal inflammation. Adherent invasive *E. coli* are largely related to inflammation in IBD. Several studies have demonstrated the therapeutic effects of bacteriophages targeting adherent invasive *E. coli* in IBD [134, 135]. Taking advantage of these findings, we can characterize and employ specific phage species to fight against IBD.

Research efforts in virome-targeted therapeutics in IBD

Phage therapy

The altered gut virome present before inflammation occurs has been emphasized. Remodeling of the gut virome before the onset of IBD is crucial. Therefore, methods for optimizing the gut virome should be considered. Phage therapy was used to treat bacterial infections before antibiotics were developed. This approach has been revisited because it has higher selectivity than antibiotics [136]. The application of phage therapy generally involves the modification of the gut bacteriome, and phage therapy suggests favorable safety and efficacy in suppressing intestinal inflammation [134]. Specific virus–bacteria interactions in IBD would be a possible breakthrough point for future research on phage therapy. Based on the accurate identification of alterations in the microbiota, customized phage therapy is expected to improve disease outcomes in IBD. Along with targeting the disease-related bacteriome, one important therapeutic goal in IBD is to restore the altered phageome. Challenges remain in defining the phages that are the primary targets of virus-directed intervention.

The development of treatments for IBD using phage-derived lytic enzymes represents an innovative approach to manage the chronic condition. Phage-derived lytic enzymes, particularly endolysins, are proteins produced by bacteriophages that degrade bacterial cell walls, leading to bacterial lysis [137]. Previously, to combat *Clostridium difficile* (*C. difficile*) infection, an endolysin derived from a novel bacteriophage was developed, which is effective against 30 diverse *C. difficile* strains, while sparing beneficial gut bacteria [138]. This provided clues of the therapeutic potential of phage-derived enzymes. *Enterococcus faecalis* (*E. faecalis*) colonization has been proved to be an inducer of IBD pathologies [139]. Recently, researchers from Japan explored the crucial role of anti-*E. faecalis* enzyme in fighting against acute graft-versus-host disease (aGVHD) [140]. They isolated highly pathogenic, cytolysin-positive *E. faecalis* from aGVHD patient fecal samples and identified an anti-*E. faecalis* enzyme derived from *E. faecalis*-specific bacteriophages. In gnotobiotic mice induced with aGVHD and colonized with *E. faecalis* or patient fecal samples dominated by *Enterococcus*, treatment with the *E. faecalis*-specific enzyme significantly decreased levels of intestinal cytolysin-positive *E. faecalis* and improved survival compared to the control group. The phage-derived lytic enzymes have shown potential in selectively targeting pathogenic bacteria in the gut, thus possibly reducing the microbial imbalances associated with IBD. All in all, research indicates that certain gut bacteria play a crucial role in the onset and progression of IBD. In the future, phage-derived enzymes may help in modulating the gut microbiome by specifically eliminating harmful bacteria while preserving beneficial microbial populations in IBD.

In addition to their antimicrobial properties, phage-derived lytic enzymes may have anti-inflammatory effects. In cutaneous T-cell lymphoma, one recombinant endolysin inhibits *Staphylococcus aureus* (*S. aureus*) growth and skin colonization. It also reduces *S. aureus*-induced inflammatory markers and suppresses tumor-promoting effects on malignant T cells [141]. In IBD patients, the enzymes can be engineered to target specific bacterial strains implicated in the disease, providing a more tailored and less invasive alternative to traditional antibiotics. As this field evolves, further studies are needed to assess long-term safety and evaluate the efficacy of these enzymes in clinical settings. The potential of phage-derived lytic enzymes offers a promising new frontier in the treatment of IBD, with fewer side effects compared to conventional therapies.

Fecal virome transplantation (FVT)

Fecal microbiota transplantation (FMT) involves transferring feces from a healthy donor to a recipient to alter the gut microbiota [142], showing promise for treating conditions like IBD [143–145]. The gut virome, a key microbiota component, may influence FMT success [146], with stable phage properties correlating more with positive outcomes than bacterial changes, and the stability of the virome may be used to predict the effect of FMT [147]. A pilot study demonstrated that even when bacterial components were removed, donor feces effectively treated recurrent *Clostridium difficile* infections, highlighting the virome's potential role in FMT efficacy, independent of bacterial components [143, 148].

Recent studies on FVT have increased the possibility of using FVT as a novel therapy for certain diseases, such as IBD [149]. Chehoud et al. attempted the transplantation of fecal materials from one donor into three children with UC within 6–12 weeks [150]. Beneficial effects have also been observed in these patients. Additionally, sequencing of virus-like particles revealed the transfer of several phage communities, such as temperate phages, which could enable breakthroughs in the treatment of UC [151]. Researchers have reported elevated caudoviral levels in patients with IBD. A recent study indicated that FMT increased the abundance of *Caudovirales* in humans with UC who responded to FMT therapy [109]. How the gut virome acts during disease onset remains unclear. Therefore, using FMT and FVT for IBD faces barriers. Comprehensive component-based research is necessary to validate the effectiveness of these new therapies. Targeted transplantation of beneficial viral communities may be superior to FMT in patients.

Conclusions

In this review, we examined the available research on IBD and the gut virome. Recent studies have highlighted the gut virome's crucial role in maintaining intestinal homeostasis. This distinct aspect of the gut microbiota could lead to novel approaches for preventing, diagnosing, and treating IBD. Recent studies have identified molecular markers with significant diagnostic potential [152]. Our research indicates that enterogenous microbiotic markers are effective for differentiating inflammatory bowel disease [153]. Additionally, the virome colonization patterns in a healthy gut and their changes during IBD can offer new diagnostic biomarkers. Previous investigations have revealed the importance of the enteric virome as an initiator of IBD. Unfortunately, discrepancies exist in many studies, and clear classifications of the pathways involved in inflammation based on recent findings are relatively scarce. Most studies were independent and could not be used to obtain consistent conclusions. Key questions must be addressed to fully understand the virome's role in IBD pathogenesis. First, most association studies supporting causality involve fecal microbiota transplantation

rather than inoculation of specific viral strains. It is difficult to establish an etiological association when multiple microbes are involved. Additionally, changes in the diversity of phages and the presence of certain animal viruses have been linked to IBD; however, whether the virome directly predisposes patients to IBD or is just a bystander remains unknown. In patients, the gut virome displays characteristic changes that involve interactions between immunity, autophagy, and disruptions in microbial interdependence that drive IBD pathogenesis. As discussed above, in IBD, an altered gut virome, characterized by an imbalance in viral populations, may contribute to chronic inflammation and tissue damage by triggering inflammatory pathways. Moreover, viral dysbiosis in IBD patients has been implicated in the development of extra-intestinal diseases, such as obesity and diabetes, liver disease, and even malnutrition, thus establishing a potential link between gut health and broader disease mechanisms [17]. The virome-host interaction acts as a bridge, not only illuminating the pathophysiology of IBD but also offering insights into the shared molecular pathways between IBD and other chronic diseases [17, 18]. Understanding the complex role of the gut virome may lead to new therapeutic approaches, including the modulation of viral populations within the gut to mitigate IBD symptoms and prevent the onset of associated comorbidities. Finally, research on efficient strategies for IBD management is an ongoing challenge, and our focus on the virome may help guide therapeutic approaches. Analyzing altered gut viruses that may be involved in critical mechanisms of IBD has allowed to implement and optimize targeted therapies. Future research directions should involve the following: (1) A precise definition of the core gut virome. (2) More qualitative and quantitative studies on the gut virome in IBD, other intestinal diseases and extra-intestinal diseases. (3) Determine how the gut virome influences IBD patients. (4) Improving therapeutic strategies targeting the gut virome.

Abbreviations

IBD	Inflammatory bowel disease
CD	Crohn's disease
UC	Ulcerative colitis
GVD	Gut Virome Database
CHVD	Cenote Human Virome Database
MGV	Metagenomic Gut Virus Database
GPD	Gut Phage Database
NGS	Next-generation sequencing
SVG	Single-virus genomics
AI	Artificial intelligence
ML	Machine learning
VLPs	Virus-like particles
DSS	Dextran sulfate sodium
HERVs	Human endogenous retroviruses
CMV	Cytomegalovirus
EBV	Epstein–Barr virus
HBx	Hepatitis B virus X protein
MNV	Murine norovirus
IL	Interleukin
IFN	Interferon
TLR	Toll-like receptors
RVA	Rotavirus
NoV	Norovirus
DCs	Dendritic cells
TNF	Tumor necrosis factor
CAR	Coxsackie-Adenovirus Receptor
aGVHD	Acute graft-versus-host disease
FVT	Fecal virome transplantation
FMT	Fecal microbiota transplantation

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Authors' contributions
HZ and TZ designed and conceived this manuscript. Y-SW and RC wrote and revised the manuscript, who contributed equally to this work. HL, L-LL, Y-BJ and AP made contributions to the revising of the manuscript. HZ and TZ critically revised the manuscript and contributed to the final draft. All authors read and approved the final manuscript.

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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

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The authors declare no competing interests.

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