Relationship between the Gut Virome and Metabolic Pathologies

Subjects: Others

Contributor: Shahrzad Ezzatpour, Alicia del Carmen Mondragon Portocarrero, Alejandra Cardelle-Cobas, Alexandre Lamas, Aroa López-Santamarina, José Manuel Miranda, Hector C. Aguilar

The human gastrointestinal tract contains large communities of microorganisms that are in constant interaction with the host, playing an essential role in the regulation of several metabolic processes. Human adenovirus infection was identified as a significant risk factor for the progression of nonalcoholic fatty liver disease (NAFLD). Furthermore, in liver cirrhosis, gut virome (GV) alterations correlate with cirrhosis progression. The most widely investigated matter is the relationship between the GM and intestinal diseases, primarily inflammatory bowel disease (IBD), although there is also a potential relation between GV and type 1 diabetes (T1D), type 2 diabetes (T2D), obesity, hypertension, malnutrition and low growth rate, metabolic syndrome, liver diseases, colorectal cancer (CRC), melanoma, cognitive maintenance, and cerebral ischemia.

Keywords: fecal viral transference ; virome ; obesity ; diabetes ; inflammatory bowel disease

1. Metabolic Syndrome

A variety of conditions that occur simultaneously and increase the risk of heart disease, stroke, and T2D are referred to as metabolic syndrome. These conditions include increased blood pressure, hyperglycemia, excess body fat around the waist, and elevated cholesterol or triglyceride levels [1]. The main factor influencing the development of metabolic syndrome is diet, which has been reported to affect the GM, including the GV [2].

Since the GM is a relevant player in the development of metabolic syndrome, it is reasonable to think that phages infecting these bacteria may also play an important role in metabolic syndrome by regulating such bacterial populations [3]. A recent study has shown that metabolic syndrome is associated with decreases in GV richness and diversity in a manner correlated with bacterial population patterns [3]. Dietary changes that cause a reduction in bacterial diversity have a direct consequence on GV diversity because there are bacterial species that are depleted from the GM and are therefore less accessible for predation by viruses. A recent study found that phages infecting Ruminococcaceae, Clostridiaceae, Bacteroidaceae, and Streptococcaceae predominated in the GV of patients with metabolic syndrome, whereas Bifidobacteriaceae phages were less abundant in patients with metabolic syndrome than in control samples [3]. Such results could reflect unequal predation by phages among the corresponding bacterial families in the gut [3]. This fact is interesting because bacteria of the genus *Bifidobacterium* inhibit the colonization of harmful intestinal bacteria, regulate the immune system, and exhibit anti-obesity and anti-inflammatory activities, thus preventing the progression of metabolic syndrome [4]. The identification of Bifidobacteriaceae species and their phages as more abundant among healthy controls is in line with established studies showing the depletion of these families in metabolic syndrome [5] and disease states associated with metabolic syndrome [6].

Furthermore, viral phages were significantly more prevalent in the GV of controls than in metabolic syndrome patients [3]. This apparent depletion of viral phages in GVs from metabolic syndrome patients may indicate a decrease in their infectivity and could be considered a link between this prominent human gut phage order and a disease state [3]. In contrast to what was reported by [3], the richness and diversity of the GV of children with metabolic syndrome were higher than those of normal-weight children without metabolic syndrome, along with an increased abundance of *Myoviridae* [1] (**Table 1**).

Table 1. Research works investigating the relationship between the gut virome and metabolic diseases.

Disease/Model	Subjects	Determination	Main Findings	References
Obesity/humans	128 obese subjects and 101 lean subjects	Gut virome (GV), bacteriome, and viral–bacterial correlations	-Obese subjects, especially those with type 2 diabetes (T2D), had a lower gut viral richness and diversity than lean controls. -GV may play an important role in the development of obesity and T2D. -Eleven viruses, including *Escherichia* phage, *Geobacillus* phage, and *Lactobacillus* phage, were higher in obese subjects than in lean controls.	[7]
Inflammatory Bowel disease (IBD)/humans	12 household controls, 18 Crohn's disease patients, and 42 ulcerative colitis patients	Stool samples investigated by virus-like particle enrichment and sequencing as well as bacterial 16S rRNA gene analysis	-Patients with IBD showed a significant increase in *Caudovirales* bacteriophages in their GV. -Changes in the GV may contribute to intestinal inflammation and bacterial dysbiosis.	[8]
Cirrhosis and hepatic encephalopathy/humans	40 controls and 163 cirrhotic patients	Stool metagenomics for bacteria and phages were analyzed in controls versus cirrhosis, within cirrhotic, hospitalized/not, and pre/post rifaximin	-Bacterial α-/β-diversity worsened from controls through cirrhosis patients. Phage α-diversity was similar in both groups. -No changes in α-/β-diversity of phages or bacteria were seen after postrifaximin treatment in cirrhotic patients.	[1]
Obesity and metabolic syndrome/humans	28 school-aged children (10 with normal weight, 10 obese, and 8 obese + metabolic syndrome)	Characterization of the gut DNA virome using metagenomic sequencing	-Phage richness and diversity of individuals with obese and obese + metabolic syndrome tended to increase with respect to controls. -The abundance of some phages correlated with gut bacterial taxa and with anthropometric and biochemical parameters altered in obese and obese + metabolic syndrome.	[9]
Bile acid metabolism/mice	7 germ-free C57BL/6J mice	Phage-induced repression of a tryptophan-rich sensory protein and repression of bile acid deconjugation	-Phages' presence in the gut can affect the microbial metabolism of bile acids. -Phague BV01 and other phages from the family *Salyersviridae* are ubiquitous in the human gut, can infect a broad range of Bacteroides hosts, and affect bile acid metabolism.	[10]
Cerebral ischemia/mice	6 adult C57BL/6J mice	Determination of GV composition by shotgun metagenomics in fecal samples	-Following focal ischemia, the abundances of two viral taxa decreased, and those of five viral taxa increased compared with previous cohorts. -Abundances of Clostridia-like phages and Erysipelatoclostridiaceae-like phages were decreased in the stroke compared with previous cohorts	[11]

Disease/Model	Subjects	Determination	Main Findings	References
IBD/humans	40 fecal samples	Stool samples investigated by bioinformatics viral sequencing and bacterial 16S rRNA gene analysis	-Changes in GV and increased numbers of temperate phage sequences were found in individuals with Crohn's disease. -Incorporating both bacteriome and GV composition offered better discrimination power between health and disease.	[3]
Metabolic syndrome/humans	196 participants with metabolic syndrome preceding cardiometabolic disease	Bulk whole genome and virus-like particle communities	-GV from metabolic syndrome patients exhibited low richness and diversity. -Viral clusters revealed that *Candidatus Heliusviridae*, a highly widespread gut phage, was found in >90% of metabolic syndrome patients.	[12]
Environmental enteric dysfunction and low growth rate/humans	94 children without diarrhea or human immunodeficiency virus	Gut bacterial and GV sequencing and analysis	- Three differentially abundant phages were identified in GV, depending on child growth velocities. -A positive correlation was found between bacteria and bacteriophage richness in children with subsequent adequate/moderate growth.	[13]
IBD/humans	Fecal samples from 24 children, 12 with inflammatory bowel disease and 12 controls	Identification of viral sequences and bacterial microbiota sequencing	-*Caudovirales*' relative abundance was greater than that of *Microviridae* in both inflammatory bowel disease patients and healthy controls. -*Caudovirales* was more abundant in Chron´s disease patients than in ulcerative colitis patients, but not than in control patients. -Pediatric inflammatory bowel disease patients can be distinguished from healthy controls by bacterial community composition.	[14]
Crohn´s disease/mice	12–23 BALB/CYJ mice	Disruption of normal resident microbiota with streptomycin sulphate administration and phage therapy	-A single day of treatment with a phage cocktail significantly decreased the number of adherent invasive *Escherichia coli* in feces. -A single dose of the phage cocktail reduced dextran sodium sulphate-induced colitis symptoms in mice.	[15]
Colorectal cancer (CRC) and colonic adenoma/humans	71 colorectal cancer patients, 63 adenoma patients, and 91 healthy controls	Metagenomic sequencing of the gut microbiome and microbial interactions in adenoma and colorectal cancer patients	-Uncultured CrAssphage was higher in healthy controls and positively associated with beneficial butyrate-producing bacteria in gut microbiota (GM). -GV was much more dynamic than the GM as the disease progressed.	[16]
CRC/humans	90 human subjects, (30 healthy controls, 30 of whom had adenomas, and 30 of whom had carcinomas)	Stool samples analyzed by 16S rRNA gene, whole shotgun metagenomics, and purified virus metagenomic sequencing	-The CRC-associated GV consisted primarily of temperate bacteriophages. -Phages influenced cancer by directly modulating the influential bacteria.	[17]

Disease/Model	Subjects	Determination	Main Findings	References
Enteric pathogens/mice	100 C57BL/6J mice	Viruses generated from molecular clones were used to infect cell lines to liberate virions. Subsequently, clones were used to infect mice that were euthanized and investigated for results of viral infections	-Chronic murine astrovirus complements defects in adaptive immunity by elevating cell-intrinsic IFN-λ in the intestinal epithelial barrier in immunodeficient mice. -Elements of the GV can protect against enteric pathogens in an immunodeficient host.	[18]
Alcoholic hepatitis/humans	89 patients with alcoholic hepatitis, 36 with alcohol use disorder, and 17 healthy people as controls	Metagenomic sequencing of virus-like particles from fecal samples, fractionated using differential filtration techniques	-Patients with alcohol use disorder showed increased viral diversity in fecal samples compared to controls and patients with alcoholic hepatitis. -History of antibiotic treatment was associated with higher GV diversity. -Specific viral taxa, such as *Staphylococcus* phages and *Herpesviridae*, were associated with increased hepatic disease severity.	[19]
Viral entities/humans	662 samples from 1-year-old children	Processing of metagenomics and metaviromics datasets	-Viral enrichment during sample processing showed a loss of a significant part of the GV and did not represent integrated bacteria containing dormant phages (prophagues). -Approximately 65–83% of the viral populations in the metavirome were not aligned with the metagenome data.	[20]
Nonalcoholic fatty liver diseases (NAFLD)/humans	73 patients with NAFLD	RNA and DNA virus-like particles from fecal samples	-Patients with NAFLD and cirrhosis showed a significant decrease in intestinal viral diversity compared with controls. -Advanced NAFLD was associated with a reduction in the proportion of phages compared with other intestinal viruses.	[21]
IBD/humans	54 Patients with IBD and 23 healthy controls	Virus-like particles were purified from stool samples and characterized by DNA and RNA sequencing and VLP particle counts	-Viral populations associated with IBD showed perturbations with respect to healthy controls. -*Anelloviridae* showed a higher prevalence in IBD compared to healthy controls, and *Analloviridae* DNA levels were biomarkers of the effectiveness of immunosuppression. -IBD subjects had a higher ratio of *Caudovirales* to *Microviridae* phages compared to healthy controls.	[22]

Disease/Model	Subjects	Determination	Main Findings	References
CRC/humans	80 colorectal primary tumors tissues and corresponding normal colorectal tissues	GV and bacteriome analysis for CRC tissues	-The number of viral species increased whereas bacterial species decreased in CRC tissues compared with healthy ones. -Phages were the most preponderant viral species in CRC tissues, and the main families were *Myoviridae*, *Siphoviridae*, and *Podoviridae*. -Primary CRC tissues were enriched for Enterobacteria, *Bacillus*, *Proteus*, and *Streptococcus* phages, together with their pathogenic hosts in contrast to normal tissues.	[23]
Type 2 diabetes (T2D)/humans	71 T2D patients and 74 healthy controls	Whole-community metagenomic sequencing data of fecal samples	-Significant increase in the number of gut phages in fecal samples was found in the T2D group. -Significant alterations of the gut phageome cannot be explained simply by covariation with the altered bacterial hosts.	[24]
Cognitive maintenance/humans	120 subjects, 60 with obesity and 60 without obesity	Neuropsychological assessment in humans, extraction of fecal genomic DNA and whole-genome shotgun sequencing	-GV was dominated by *Caudovirales* and *Microviridae* phages. -Subjects with increased *Caudovirales* and *Siphoviridae* levels in the gut microbiome performed better cognitive status. -Phages should be considered novel actors in the microbiome–brain axis.	[24]
Cognitive maintenance/mice	11 mice were orally gavaged with saline and fecal material from humans	Behavioral testing in mice and study of gene expression in mouse prefrontal cortex	-Microbiota transplantation from human donors with increased specific *Caudovirales* levels led to increased scores in novel object recognition. -Phages should be considered novel actors in the microbiome–brain axis.	[25]
CRC/humans	74 patients with CRC and 92 healthy controls	Shotgun metagenomic analyses of viromes of fecal samples	-Gut phage community diversity was significantly increased in patients with CRC compared with controls. -GV dysbiosis was associated with early- and late-stage CRC.	[26]
Fructose intake/mice	25 C57BL/6J mice per group were used for phage production, and 36 mice were used for the in vivo dietary crossover study	*Lactobacillus reuteri* survival and phage production during gastrointestinal transit in mice	-Fructose intake activated the Ack pathway, involved in generating acetic acid, which promotes phage production.	[27]
Malnutrition/humans	8 monozygotic and 12 dizygotic twin pairs	Shotgun pyrosequencing of VLP-derived DNA	-Phage plus members of the *Anelloviridae* and *Circoviridae* families of eukaryotic viruses discriminate discordant from concordant healthy pairs.	[28]

Disease/Model	Subjects	Determination	Main Findings	References
Type 1 diabetes (T1D)/humans	103 T1D children and their mothers	Determination of virus antibodies, enterovirus RNA, and enzyme immunoassay analysis	-Autoantibody-positive children had more enterovirus infections than autoantibody-negative children before the appearance of autoantibodies. -Enterovirus infections seem to be associated with the induction of β-cell autoimmunity in young children with increased genetic susceptibility to T1D.	[29]
High-fat diet/mice	12 C57BL/6J pregnant female mice	Mice were administered with subtherapeutic antibiotic dosages or no antibiotic and subsequently analyzed for GV composition and 16S rRNA metagenomics	-High-fat diet significant shift away from the relatively abundant *Siphoviridae*, accompanied by increases in phages from the *Microviridae* family. -Phage structural genes significantly decreased after the transition to a high-fat diet.	[30]
IBD/humans and mice	Fecal samples collected from 3 ulcerative colitis patients in remission and 3 unrelated healthy controls were transferred to C57BL/6 mice	Fecal virus-like particles (VLPs) isolated from ulcerative colitis patients and healthy controls were transferred to mice	-VLPs isolated from ulcerative colitis patients specifically altered the relative abundances of several bacterial taxa involved in IBD progression in mice. -Phages are dynamic regulators of GM and implicate the GV in modulating intestinal inflammation and disease.	[31]
T1D/humans	Fecal samples from 11 children who had developed serum autoantibodies associated with T1D and healthy controls	Detection of phage and eukaryotic viral sequences	-GV of T1D subjects was less diverse than those of controls. Lower phage diversity in cases than in controls. -Specific components of the GV were both directly and inversely associated with the development of human autoimmune disease. -Among eukaryotic viruses, there was a significant enrichment of *Circoviridae*-related sequences in controls in comparison with T1D patients.	[32]
Hypertension/humans	196 samples	Viral and bacterial metagenomic investigation of fecal samples	-Virus could have higher discrimination power than bacteria to differentiate healthy prehypertension samples from hypertension patients	[33]

2. Obesity, Diabetes and Malnutrition

Obesity and diabetes are two forms of metabolic diseases that are highly prevalent worldwide [31]. In recent decades, there has been substantial evidence that abnormalities in GM composition can play a major role in the development of both diseases, although most evidence refers to gut bacterial composition and activities [34]. However, recent findings found significant differences in some viral families between obese and diabetic patients with respect to healthy patients in children [28][32] and mouse models [35].

A recent study found that both viral richness and diversity in the GV were lower than those found for lean subjects and in obese patients with T2D compared to lean controls [31]. Surprisingly, these results are contradictory to those previously reported by Ma et al. [23], who found a higher phage richness in T2D patients than in nondiabetic controls, as well as an increased relative abundance of the families *Siphoviridae*, *Podoviridae*, and *Myoviridae* and the unclassified order *Caudovirales* in T2D patients [23]. Previous Enterovirus infection was found to be a risk factor for T1D in children [28].

Afterward, another study showed a higher prevalence of the families *Circoviridae* and *Picornaviridae* in T1D pediatric patients than in healthy children [32]

High-fat-diet-induced obese mice showed a significant reduction in the family *Siphoviriade* and an increase in the virus families *Microviridae*, *Phycodnaviridae*, and *Miniviridae* in the fecal virome [29]. Rasmussen et al. [35] proposed GV modification as a potential therapeutic strategy against T1D and obesity. To verify this hypothesis, VLPs were transferred from slim mice to high-fat diet-induced obese mice, and as a result, weight gain and diabetes symptoms significantly decreased in obese mice [35].

Regarding viral species, 17 were found to have significantly different proportions in obese and diabetic subjects compared with lean subjects [29]. Among them, 4 viral species (*Micromonas pusilla* virus, *Cellulophaga* phage, *Bacteroides* phage, and *Halovirus,* unclassified DNA viruses) were higher in obese and T2D patients, whereas 13 viral species, including Hokovirus, Klosneuvirus, and Catovirus, were lower in obese-plus-T2D subjects with respect to lean controls [29][31].

Malnutrition is a global health problem that affects large numbers of individuals regardless of age, gender, race, social status, and geographic boundaries. It can be defined as an imbalance between energy and nutrient intake and the individual's requirements, which can alter body measurements, compositions, and functions [36]. Children with malnutrition have been reported to have an immature gut GM composition compared to those without malnutrition. This lack of maturity in their GM is characterized by a lower α-diversity of the GM as well as a disproportionate expansion of the phylum Proteobacteria [37]. Similarly, disruption of the GV, including that of intestinal phages and eukaryotic virus members, could increase the risk of severe acute malnutrition [27]. A recent study found that phages of the order *Caudovirales* contributed differentially to stunted growth in malnutrition induced by environmental enteric dysfunction [12]. As the phylum Proteobacteria exists in a higher proportion in the GM with malnutrition relative to that of children without stunting and as *Caudovirales* phages (especially *Siphoviridae*) have Proteobacteria as one of the main bacterial hosts [38] and are also present in greater numbers in malnourished children than in healthy children, there might be a cooccurring phage-bacterial dynamic in the gut of stunted children [39], with both viruses/phages contributing to the severity of malnutrition.

3. Liver Diseases

The liver is a very important pivotal organ for host metabolism and maintains bidirectional communication with the gut via the gut–liver axis [20]. Thus, the liver plays a central role in the pathogenesis of several metabolic diseases. Recent works have investigated the potential changes in GV linked to liver diseases such as alcoholic hepatitis [18], NAFLD [20], and bile acid metabolism [9]. Additionally, although it is not a liver disease itself, the potential changes in the GV in response to the high intake of fructose are also important [26]. Beyond its lipogenic effect, fructose intake is also related to hepatic inflammation and cellular stress, such as oxidative and endoplasmic stress, which contributes to the progression of simple steatosis to nonalcoholic fatty liver disease [40].

In the case of NAFLD, patients with a more severe disease showed lower viral diversity than patients with a lower degree of disease or healthy controls [20]. At the same time, the proportion of phages among the total GV was also significantly lower in the case of severe NAFLD patients than in the less severe cases of the controls [20].

Regarding fructose intake, fructose increases the growth of *Lactobacillus reuteri*, a key important bacterial species considered an important lysogen, which are bacterial prophages inserted within their genomes that promote phage production [26]. Due to its higher sweetening power, fructose is one of the most abundant sugars consumed in a Western-style diet and results in more pronounced fructose-mediated phage production by *L. reuteri* than the intake of other sugars [26].

In the case of alcoholic liver disease, disease-specific alterations in the GV were reported, and gut viruses were identified as potent drivers of alcohol-specific liver disease [18]. In contrast to NAFLD, in alcoholic liver disease, increased viral diversity was found in patients with alcoholic liver disease, especially in those with a higher degree of alcoholic hepatitis [18]. Regarding viral proportions, the authors found an increase in eukaryotic viruses such as *Parvoviridae* and *Herpesviridae*, along with increases in intestinal phages such as Enterobacteriaceae phages, *Escherichia* phages, and *Enterococcus* phages in patients with alcoholic liver disease compared to controls [18]. Both *Parvoviridae* and *Herpesviridae* may be found in higher proportions in NAFLD subjects because they may have a depressed immune system or because the medication administered to them indirectly causes increased replication of the viruses in host cells [18]. The latter aspect regarding the relation of GV and hepatic disease is the relation of the activity of the *Bacteroides*

phage BV01, a temperate phage integrated into *Bacteroides vulgatus,* a species that can repress the microbial modification of the bile acid pool in the host, which could be linked to beneficial changes in human host metabolism [9].

4. Cancer

Although the relationship between the GV and some types of cancer, such as metastatic melanoma [41] or adenoma [15], has been investigated, most works on the relationship between the human GV and cancer have focused on colorectal cancer (CRC) [15][16][22][25][42], which is logical since it is the type of cancer that has the most direct contact with the intestinal virome. According to Wong and Yu [43], CRC is related to modifications in the GM, in which some bacterial genera, such as *Roseburia*, are potentially protective taxa, whereas other genera, such as *Bacteroides, Escherichia, Fusobacterium*, and *Porphyromona,* are considered procarcinogenic agents.

Metagenomic analysis of stool samples from CRC patients revealed an increase in the richness and diversity of the intestinal GV with respect to control patients [15][22][25]. In another case, it was found that the differences between CRC patients and controls were insufficient for identifying specific virome communities between healthy and cancerous states [16]. The fact that phage richness is higher in CRC patients was hypothesized to be due to an increase in intestinal permeability, known as a “leaky gut”, caused by this phage, which facilitates the infiltration of pathogens and triggers chronic inflammation [44]. Another study found that phages, especially those from the families *Siphoviridae* and *Myoviridae*, are vital driving factors during the transformation from a healthy intestine to intestinal adenocarcinoma and to CRC [3].

In another work, the families Inovirus and Tunalikerirus were related to the development of CRC due to their capacity to insert random oligonucleotides into the bacterial genome, stimulating the production of bacterial biofilms and thus contributing to the carcinogenesis of the colon [45]. Both families are known to infect gram-negative bacterial hosts, including enterotoxigenic *Bacteroides fragilis*, *Fusobacterium nucleatum*, and genotoxic *Escherichia coli*, bacterial species often implicated in CRC development [25].

Another recent study of the GV in bulk from CRC patients reported significant reductions in Enterobacteria phages and CrAssphages compared to healthy controls [15]. Some viral species were reported to have the potential to act as discriminant markers of CRC; Orthobunyavirus, Tunalikevirus, Phikzlikevirus, Betabaculovirus, and Sp6likevirus were the viral genera with significantly higher abundances in CRC patients than in control patients [25].

Upon investigating primary tumor tissues of CRC, phages were found to be the most preponderant viral species, and the main families were *Myoviridae*, *Siphoviridae*, and *Podoviridae* [22][46]. The most frequently detected eukaryotic viruses include human endogenous Retrovirus K113, human Herpesviruses 7 and 6B, Megavirus chilensis, Cytomegalovirus, and Epstein-Barr virus [22]. A higher relative presence of human papillomavirus was also found in CRC versus non-CRC tissues [47]. Additionally, it was also shown that Epstein-Barr virus infection could contribute to CRC development by inducing mutagenesis in intestinal cells [22].

References

1. Bikel, S.; López-Leal, G.; Cornejo-Granados, F.; Gallardo-Becerra, L.; García-López, R.; Sánchez, F.; Equihua-Medina, E.; Ochoa-Romo, J.P.; López-Contreras, B.E.; Canizales-Quinteros, S.; et al. Gut dsDNA virome shows diversity and richness alterations associated with childhood obesity and metabolic syndrome. iScience 2021, 24, 102900.
2. Minot, S.; Sinha, R.; Chen, J.; Li, H.; Keilbaugh, S.A.; Wu, G.D.; Lewis, J.D.; Bushman, F.D. The human gut virome: Inter-individual variation and dynamic response to diet. Genome Res. 2011, 21, 1616–1625.
3. de Jonge, P.A.; Wortelboer, K.; Scheithauer, T.P.M.; van den Born, B.J.H.; Zwinderman, A.H.; Nobrega, F.L.; Dutilh, B.E.; Nieuwdorp, M.; Herrema, H. Gut virome profiling identifies a widespread bacteriophage family associated with metabolic syndrome. Nat. Commun. 2022, 13, 3594.
4. Zuo, T.; Wong, S.H.; Lam, K.; Lui, R.; Cheung, K.; Tang, W.; Ching, J.Y.L.; Chan, P.K.S.; Chan, M.C.W.; Wu, J.C.Y.; et al. Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. Gut 2018, 67, 634–643.
5. Haro, C.; Garcia-Carpintero, S.; Alcala-Diaz, J.F.; Gomez-Delgado, F.; Delgado-Lista, J.; Perez-Martinez, P.; Rangel Zuñiga, O.A.; Quintana-Navarro, G.M.; Landa, B.B.; Clemente, J.C.; et al. The gut microbial community in metabolic syndrome patients is modified by diet. J. Nutr. Biochem. 2016, 27, 27–31.

6. Aron-Wisnewsky, J.; Vigliotti, C.; Witjes, J.; Le, P.; Holleboom, A.G.; Verheij, J.; Nieuwdorp, M.; Clément, K. Gut microbiota and human NAFLD: Disentangling microbial signatures from metabolic disorders. Nat. Rev. Gastroenterol. Hepatol. 2020, 17, 279–297.
7. Norman, J.M.; Handley, S.A.; Baldridge, M.T.; Droit, L.; Liu, C.Y.; Keller, B.C.; Kambal, A.; Monaco, C.L.; Zhao, G.; Fleshner, P.; et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell 2015, 160, 447–460.
8. Bajaj, J.S.; Sikaroodi, M.; Shamsaddini, A.; Henseler, Z.; Santiago-Rodriguez, T.; Acharya, C.; Fagan, A.; Hylemon, P.B.; Fuchs, M.; Gavis, E.; et al. Interaction of bacterial metagenome and virome in patients with cirrhosis and hepatic encephalopathy. Gut 2021, 70, 1162–1173.
9. Campbell, D.E.; Ly, L.K.; Ridlon, J.M.; Hsiao, A.; Whitaker, R.J.; Degnan, P.H. Infection with bacteroides phage bv01 alters the host transcriptome and bile acid metabolism in a common human gut microbe. Cell Rep. 2020, 32, 108142.
10. Chelluboina, B.; Kieft, K.; Breister, A.; Anantharaman, K.; Vemuganti, R. Gut virome dysbiosis following focal cerebral ischemia in mice. J. Cereb. Blood Flow Metab. 2022, 42, 1597–1602.
11. Clooney, A.G.; Sutton, T.D.S.; Shkoporov, A.N.; Holohan, R.K.; Daly, K.M.; O'Regan, O.; Ryan, F.J.; Draper, L.A.; Plevy, S.E.; Ross, R.P.; et al. Whole-virome analysis sheds light on viral dark matter in inflammatory bowel disease. Cell Host Microbe 2019, 26, 764–778.e5.
12. Desai, C.; Handley, S.A.; Rodgers, R.; Rodriguez, C.; Ordiz, M.I.; Manary, M.J.; Holtz, L.R. Growth velocity in children with environmental enteric dysfunction is associated with specific bacterial and viral taxa of the gastrointestinal tract in Malawian children. PLoS Negl. Trop. Dis. 2020, 14, e0008387.
13. Fernandes, M.A.; Verstraete, S.G.; Phan, T.; Deng, X.; Stekol, E.; Lamere, B.; Lynch, S.V.; Heyman, M.B.; Delwart, E. Enteric virome and bacterial microbiota in children with ulcerative colitis and crohn disease. J. Pediatr. Gastroenterol. Nutr. 2019, 68, 30–36.
14. Galtier, M.; De Sordi, L.; Sivignon, A.; de Vallée, A.; Maura, D.; Neut, C.; Rahmouni, O.; Wannerberger, K.; Darfeuille-Michaud, A.; Desreumaux, P.; et al. Bacteriophages targeting adherent invasive Escherichia coli strains as a promising new treatment for Crohn's disease. J. Crohn's Colitis 2017, 11, 840–847.
15. Gao, R.; Zhu, Y.; Kong, C.; Xia, K.; Li, H.; Zhu, Y.; Zhang, X.; Liu, Y.; Zhong, H.; Yang, R.; et al. Alterations, interactions, and diagnostic potential of gut bacteria and viruses in colorectal cancer. Front. Cell. Infect. Microbiol. 2021, 11, 657867.
16. Hannigan, G.D.; Duhaime, M.B.; Ruffin, M.T., IV; Koumpouras, C.C.; Schloss, P.D. Diagnostic potential and interactive dynamics of the colorectal cancer virome. mBio 2018, 9, e02248-18.
17. Ingle, H.; Lee, S.; Ai, T.; Orvedahl, A.; Rodgers, R.; Zhao, G.; Sullender, M.; Peterson, S.T.; Locke, M.; Liu, C.-T.; et al. Viral complementation of immunodeficiency confers protection against enteric pathogens via interferon-λ. Nat. Microbiol. 2019, 4, 1120–1128.
18. Jiang, L.; Lang, S.; Duan, Y.; Zhang, X.; Gao, B.; Chopyk, J.; Schwanemann, L.K.; Ventura-Cots, M.; Bataller, R.; Bosques-Padilla, F.; et al. Intestinal virome in patients with alcoholic hepatitis. Hepatology 2020, 72, 2182–2196.
19. Johansen, J.; Plichta, D.R.; Nissen, J.N.; Jespersen, M.L.; Shah, S.A.; Deng, L.; Stokholm, J.; Bisgaard, H.; Nielsen, D.S.; Sørensen, S.J.; et al. Genome binning of viral entities from bulk metagenomics data. Nat. Commun. 2022, 13, 965.
20. Lang, S.; Demir, M.; Martin, A.; Jiang, L.; Zhang, X.; Duan, Y.; Gao, B.; Wisplinghoff, H.; Kasper, P.; Roderburg, C.; et al. Intestinal virome signature associated with severity of nonalcoholic fatty liver disease. Gastroenterology 2020, 159, 1839–1852.
21. Liang, G.; Conrad, M.A.; Kelsen, J.R.; Kessler, L.R.; Breton, J.; Albenberg, L.G.; Marakos, S.; Galgano, A.; Devas, N.; Erlichman, J.; et al. Dynamics of the stool virome in very early onset inflammatory bowel disease. J. Crohn's Colitis 2020, 14, 1600–1610.
22. Marongiu, L.; Landry, J.J.M.; Rausch, T.; Abba, M.L.; Delecluse, S.; Delecluse, H.J.; Allgayer, H. Metagenomic analysis of primary colorectal carcinomas and their metastases identifies potential microbial risk factors. Mol. Oncol. 2021, 15, 3363–3384.
23. Ma, Y.; You, X.; Mai, G.; Tokuyasu, T.; Liu, C. A human gut phage catalog correlates the gut phageome with type 2 diabetes. Microbiome 2018, 6, 24.
24. Mayneris-Perxachs, J.; Castells-Nobau, A.; Arnoriaga-Rodríguez, M.; Garre-Olmo, J.; Puig, J.; Ramos, R.; Martínez-Hernández, F.; Burokas, A.; Coll, C.; Moreno-Navarrete, J.M.; et al. Caudovirales bacteriophages are associated with improved executive function and memory in flies, mice, and humans. Cell Host Microbe 2022, 30, 340–356.e8.
25. Nakatsu, G.; Zhou, H.; Wu, W.K.K.; Wong, S.H.; Coker, O.O.; Dai, Z.; Li, X.; Szeto, C.H.; Sugimura, N.; Lam, T.Y.T.; et al. Alterations in enteric virome are associated with colorectal cancer and survival outcomes. Gastroenterology 2018,

155, 529–541.e5.

26. Oh, J.H.; Alexander, L.M.; Pan, M.; Schueler, K.L.; Keller, M.P.; Attie, A.D.; Walter, J.; van Pijkeren, J.P. Dietary fructose and microbiota-derived short-chain fatty acids promote bacteriophage production in the gut symbiont Lactobacillus reuteri. Cell Host Microbe 2019, 25, 273–284.e6.
27. Reyes, A.; Blanton, L.V.; Cao, S.; Zhao, G.; Manary, M.; Trehan, I.; Smith, M.I.; Wang, D.; Virgin, H.W.; Rohwer, F.; et al. Gut DNA viromes of Malawian twins discordant for severe acute malnutrition. Proc. Natl. Acad. Sci. USA 2015, 112, 11941–11946.
28. Sadeharju, K.; Hämäläinen, A.-M.; Knip, M.; Lönnrot, M.; Koskela, P.; Virtanen, S.M.; Ilonen, J.; Åkerblom, H.K.; Hyöty, H. Enterovirus infections as a risk factor for type I diabetes: Virus analyses in a dietary intervention trial. Clin. Exp. Immunol. 2003, 132, 271–277.
29. Schulfer, A.; Santiago-Rodriguez, T.M.; Ly, M.; Borin, J.M.; Chopyk, J.; Blaser, M.J.; Pride, D.T. Fecal viral community responses to high-fat diet in mice. mSphere 2020, 5, e00833-19.
30. Sinha, A.; Li, Y.; Mirzaei, M.K.; Shamash, M.; Samadfam, R.; King, I.L.; Maurice, C.F. Transplantation of bacteriophages from ulcerative colitis patients shifts the gut bacteriome and exacerbates the severity of DSS colitis. Microbiome 2022, 10, 105.
31. Yang, K.; Niu, J.; Zuo, T.; Sun, Y.; Xu, Z.; Tang, W.; Liu, Q.; Zhang, J.; Ng, E.K.W.; Wong, S.K.H.; et al. Alterations in the gut virome in obesity and type 2 diabetes mellitus. Gastroenterology 2021, 161, 1257–1269.e13.
32. Zhao, G.; Vatanen, T.; Droit, L.; Park, A.; Kostic, A.D.; Poon, T.W.; Vlamakis, H.; Siljander, H.; Härkönen, T.; Hämäläinen, A.-M.; et al. Intestinal virome changes precede autoimmunity in type I diabetes-susceptible children. Proc. Natl. Acad. Sci. USA 2017, 114, E6166–E6175.
33. Han, M.; Yang, P.; Zhong, C.; Ning, K. The Human Gut Virome in Hypertension. Front. Microbiol. 2018, 9, 3150.
34. Pascale, A.; Marchesi, N.; Govoni, S.; Coppola, A.; Gazzaruso, C. The role of gut microbiota in obesity, diabetes mellitus, and effect of metformin: New insights into old diseases. Curr. Opin. Pharmacol. 2019, 49, 1–5.
35. Rasmussen, T.S.; Mentzel, C.M.J.; Kot, W.; Castro-Mejía, J.L.; Zuffa, S.; Swann, J.R.; Hansen, L.H.; Vogensen, F.K.; Hansen, A.K.; Nielsen, D.S. Faecal virome transplantation decreases symptoms of type 2 diabetes and obesity in a murine model. Gut 2020, 69, 2122–2130.
36. Khaliq, A.; Wraith, D.; Nambiar, S.; Miller, Y. A review of the prevalence, trends, and determinants of coexisting forms of malnutrition in neonates, infants, and children. BMC Public Health 2022, 22, 879.
37. Subramanian, S.; Huq, S.; Yatsunenko, T.; Haque, R.; Mahfuz, M.; Alam, M.A.; Benezra, A.; Destefano, J.; Meier, M.F.; Muegge, B.D.; et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature 2014, 510, 417–421.
38. Low, S.J.; Džunková, M.; Chaumeil, P.A.; Parks, D.H.; Hugenholtz, P. Evaluation of a concatenated protein phylogeny for classification of tailed double-stranded DNA viruses belonging to the order Caudovirales. Nat. Microbiol. 2019, 4, 1306–1315.
39. Khan Mirzaei, M.; Khan, M.A.A.; Ghosh, P.; Taranu, Z.E.; Taguer, M.; Ru, J.; Chowdhury, R.; Kabir, M.M.; Deng, L.; Mondal, D.; et al. Bacteriophages isolated from stunted children can regulate gut bacterial communities in an age-specific manner. Cell Host Microbe 2020, 27, 199–212.e5.
40. Jegatheesan, P.; De Bandt, J.P. Fructose and NAFLD: The multifaceted aspects of fructose metabolism. Nutrients 2017, 9, 230.
41. Baruch, E.N.; Youngster, I.; Ben-Betzalel, G.; Ortenberg, R.; Lahat, A.; Katz, L.; Adler, K.; Dick-Necula, D.; Raskin, S.; Bloch, N.; et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science 2021, 371, 602–609.
42. Zheng, D.W.; Dong, X.; Pan, P.; Chen, K.W.; Fan, J.X.; Cheng, S.X.; Zhang, X.Z. Phage-guided modulation of the gut microbiota of mouse models of colorectal cancer augments their responses to chemotherapy. Nat. Biomed. Eng. 2019, 3, 717–728.
43. Wong, S.H.; Yu, J. Gut microbiota in colorectal cancer: Mechanisms of action and clinical applications. Nat. Rev. Gastroenterol. Hepatol. 2019, 16, 690–704.
44. Tetz, G.; Tetz, V. Bacteriophage infections of microbiota can lead to leaky gut in an experimental rodent model. Gut Pathog. 2016, 8, 33.
45. Johnson, C.H.; Dejea, C.M.; Edler, D.; Hoang, L.T.; Santidrian, A.F.; Felding, B.H.; Ivanisevic, J.; Cho, K.; Wick, E.C.; Hechenbleikner, E.M.; et al. Metabolism links bacterial biofilms and colon carcinogenesis. Cell Metab. 2015, 21, 891–897.

46. Cepko, L.C.S.; Garling, E.E.; Dinsdale, M.J.; Scott, W.P.; Bandy, L.; Nice, T.; Faber-Hammond, J.; Mellies, J.L. Myoviridae phage PDX kills enteroaggregative Escherichia coli without human microbiome dysbiosis. J. Med. Microbiol. 2020, 69, 309–323.
47. Massimino, L.; Lovisa, S.; Antonio Lamparelli, L.; Danese, S.; Ungaro, F. Gut eukaryotic virome in colorectal carcinogenesis: Is that a trigger? Comput. Struct. Biotechnol. J. 2021, 19, 16–28.