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Gut Virome–Host Interactions: Implications for Immunity and Therapeutic Response

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Abstract

The gut virome, which primarily consists of bacteriophages and eukaryotic viruses, plays a crucial role in maintaining human health and regulating the immune system. This review examines the formation of the virome at birth, its dynamic transformation throughout life, and its interactions with the microbiome and host immunity. Special attention is paid to the role of dysbiosis and changes in the virome in the pathogenesis of such chronic diseases as inflammatory bowel disease, diabetes, and cancer. Additionally, potential therapeutic implications, such as fecal microbiota transplantation and the possible use of phage therapy, are discussed. Through a summary of recent discoveries, this paper highlights the importance of applying virome analysis as part of further studies on the role of the gut virome is essential to advance precision medicine and virotherapy

Introduction

Iraqi journal Hippocrates suggested that many diseases may originate in the digestive tract nearly 2000 years ago. At that time, we lacked scientific methods to investigate this hypothesis, yet we now demonstrate that the gut does influence our physiological well-being. Bacteriophages [Phage] comprise the dominant virus strain within gut viromes [1,2]. These are viruses that specifically infect bacteria. The discovery of bacteriophages or phages happened in 1915 and 1917 through the work of Frederick Twort and Felix D'Herelle, after which human understanding of these viruses only increased throughout the decades [3]. Research is progressively exposing the functions of phages within human health [4]. Sequencing advances, coupled with computational methods, enabled the discovery of new

phages for virome characterization in the gut [5]. The scientific community investigating microbial and medical fields shows special interest in multiple strains found within the gut virome. Human biology has always contained viruses as an essential component since the early stages of human history. Understanding basic biological ecology, together with human health, requires an increased understanding of the gut virome [6]. Scientists believe that gut virome colonization begins at birth and then develops according to various environmental factors, ultimately becoming unique for each person [7]. deleteGut dysbiosis has been associated with conditions such as diabetes, Crohn's disease, and ulcerative colitis, which can create gut dysbiosis. The health of a person suffers from gut dysbiosis, which occurs when the bacteria inside the gut lose their balance [8]. Places for tailed phage class Caudoviricetes members show substantial differences in terms of diversity and richness between dysbiotic individuals and healthy controls [9]. Treating gut dysfunction and chronic illness symptoms involves transferring a healthy person's fecal microbiome, along with integrated viruses, to achieve positive results [10].

The virome is established at birth

One of the most significant life events is birth, which also marks the beginning of the human virome. It is widely acknowledged that viral colonization in babies born by vaginal delivery [VD] or cesarean section [CS] begins as soon as they are exposed to a non-sterile environment after birth, and that the mode of birth influences the variety of viruses and phage communities present [11]. Researchers disagree intensely about how microbes initiate their residence in early development. Conclusions support the notion that prenatally seeded human microbiome development commences within the womb, as evidenced by the detection of bacterial, fungal, viral, and archaeal DNA in amniotic fluid and meconium [12]. It is possible to improve gut function through the transfer of a healthy fecal microbiome, along with its associated viral components, from a disease-free person [13]. Researchers have gathered information about enteric viral communities, examining early life development while investigating the broad health effects and relationships between gut viruses and mood disorders. A discussion of available methods for studying dark matter viruses, along with an examination of undefined virus species and detailed research directions, completes the analysis [14]. virome than those born by CS, with Caudoviricetes, Microviridae, and Anelloviridae the most abundant viruses detected [15]. The methods used for birth delivery cause disagreement about how microorganisms are shaped. When comparing birthing methods, microbiome studies using bacterial 16S sequencing did not reveal significant differences [16]. Notwithstanding, these results are the findings from a recent study involving 310 CS and 281 VD neonates who provided 1,679 gut microbiota samples through

longitudinal analysis [17]. This research presents specific, substantial microbiome differences correlated with birth mode alterations and modifications due to prenatal antibiotic treatments [18].

The gut virome changes throughout life

The intestinal virome experiences multiple transformations during the first 24 months after birth [19]. Nevertheless, the enteric virome gradually finds its makeup for every person and stays largely constant with just a few variations. Reports show up to 80% of the sequences are unaltered [20]. Ongoing health depends on the steady state of gut viral components. Stable gut microbiota relationships between microorganisms lead to better psychological well-being [21]. The microbial populations are managed by the virome through phage-bacterium interactions, which support various homeostatic functions in the body [22]. When the gut's normal function is disturbed and it enters dysbiosis, this stability is upset [23]. As demonstrated in inflammatory bowel disease, increased virome variety and richness may be a factor in gut pathogenesis [24]. Other illness states, such as C. difficile infection, type 1 diabetes, cancer, or AIDS, also significantly change the virome [25].

The Composition of the Gut Virome

The composition of the human virome varies depending on the anatomical compartment, such as the blood, GI tract, respiratory tract, skin, and urogenital system [26]. It has been estimated that the number of gut viruses in an adult human is comparable to that of gut bacteria, with over 1012 virus-like particles [VLPs] in each person, based on their body size [27]. With an estimated 109–1010 VLPs per gram of feces, the GI tract is home to the greatest number of viruses in the human body [28]. Strains from two DNA virus types form the normal DNA virome found in the adult gut .The healthy adult gut contains RNA viruses [ssRNA and dsRNA] and DNA [dsDNA] viruses [29]. Extensive research, including our studies, demonstrates individual gut virome structures are distinctive and dependent on regional factors and life choices and dietary habits as well and age group characteristics [30].

Both prokaryotic and eukaryotic viruses, which infect eukaryotic cells, mainly human cells in the gut, are present in the human gut virome [31]. Although bacterial infections prevail at approximately 90% of all viral infections, the remaining 10% consists of eukaryotic viruses, eukaryotic DNA viruses[anelloviruses, adenoviruses, herpesviruses, and others] form part of this category [32]. Under steady-state situations, eukaryotic viruses maintain inert characteristics before they activate host immunity [33]. In contrast, eukaryotic RNA viruses are uncommon in healthy individuals, and the majority of intestinal eukaryotic RNA viruses are said to be viruses found in plants [34]. When an infection causes stress in the human host, pathogenic RNA viruses may manifest in the stomach [35]. There are significantly more phages [also referred to as bacteriophages and bacterial viruses] than

eukaryotic viruses [36]. Viruses are found in the human gut and make up about 90% of the gut virome, while RNA phages are far less common [37] Figure 1]. Studies have proven that RNA phages extend their distribution further than scientists originally suspected [38]. Phages have been identified in various environmental niches, including animal excrement [39]. DNA phages make up most of the known phages present in human intestinal systems [40]. At the order level, scientists have discovered Caudovirales dsDNA viruses in the greatest quantities, while at the family level, Microviridae ssDNA viruses demonstrate the highest prevalence [41]. Just 56¢ Six percent of gut viromes were annotated at the lower taxonomic and familial levels, whereas the majority were left unannotated [42]. It was projected that viruses would fall under the Caudovirales family [43]. The International Committee on Taxonomy of Viruses [Caudovirales dsDNA] recently dissolved the Caudovirales in the phylum Caudoviricetes in 2021, and six new families, Ackermannviridae, Chaseviridae, Herelleviridae, Demerecviridae, Drexlerviridae, and Autographiviridae, have been formally accepted to take the place of the former Caudovirales order [44]. Age affects how the human gut virome's makeup changes [45]. According to a long-term analysis of the baby GI virome's makeup, early in life, bacterial, archaeal, and eukaryotic viruses were established [46].

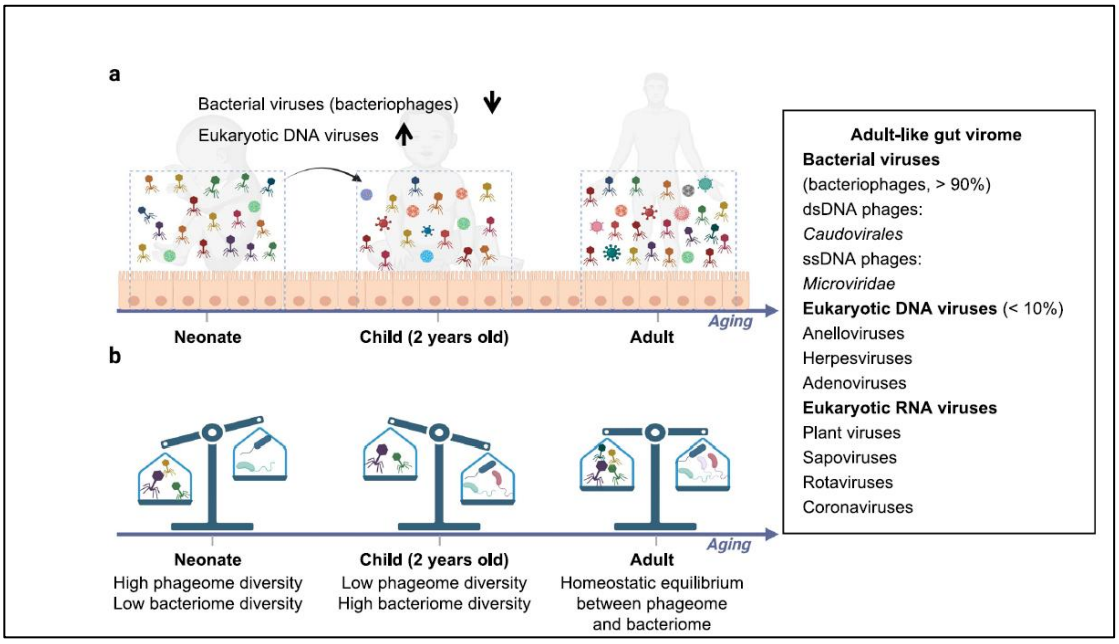

Figure 1:The human gut virome's composition. The composition of the gut virome transforms in correlation with age advancement, and it concurrently changes in diversity and richness metrics. When aging occurs, the ratio between bacteriophages and bac

The function of the gut virome

The human gut virome's function is supported by cross-kingdom interactions between phages and bacteria, as well as between viruses and phages and the host immune system [48]. In both health and

illness, Phages are naturally occurring parasites of bacteria that have the power to modify the bacteriome's composition, metabolism, evolution, and adaptation in the gut [49]. In addition, gut viruses play a critical role in the formation, growth, and operation of the human immune system [50]. As compensation, the composition and gut virome function are mutually influenced and controlled by the host immune system and the gut bacteriome [51].

Interactions between Gut Virome and Bacteriome

Phages are extensively dispersed throughout the intestinal lumen, feces, and intestinal mucosal surfaces, and they have a significant impact on the coexisting bacteria in The human intestines. Phage replication cycles play a major role in their capacity to influence the make-up of gut bacterial communities [52], Fig. 2] . Life cycles of phages fall into four distinct groups, which include lytic and temperature/lysogenic and pseudolysogenic with bacterial budding [53]. Traditional life cycles of bacterial viruses occur as either lytic or lysogenic pathways [54]. After infecting host bacteria, lytic phages distribute their genome to produce viral macromolecules and particles composition of the gut bacteriome depends strongly on biological processes that function in vital ways [55]. Environmental stress, as well as intestinal inflammation, results in the widespread occurrence of the lytic phage phenotype [56]. The life cycle of lysogenic temperate phages, which are known as lysogenic phages, executes an additional widespread replication cycle [57]. A typical behavior in temperate phages involves entering the host bacteria's chromosomes while establishing a condition of quiescence. The virus remains dormant as "prophage" during periods of quiescence while waiting for unfavorable environmental conditions to activate itself [58]. Antibiotics, UV light, temperature or pH changes, chemical or dietary inducers, and oxidative/inflammatory stressors are all potent elements that encourage phage genome excision, resulting in a transition to a lytic life cycle [59]. While many phages lack such a life cycle, prophage induction is typically phage-dependent and inducer-dependent [60]. Furthermore, in unfavorable environmental circumstances, certain phages can undergo a pseudolysogenic life cycle [61]. The phage genome is an episomal [plasmid-like] construct that does not integrate or replicate within the bacterial cell [62]. Phages of the Plasmaviridae category possess a distinct replication mechanism that enables their replication process outside host cells while protecting the bacterial host from destruction [63]. The various ways that phages work together enhance their functionality, flexibility, and stability, and as a result, the development of the human gut's bacterial populations [64].

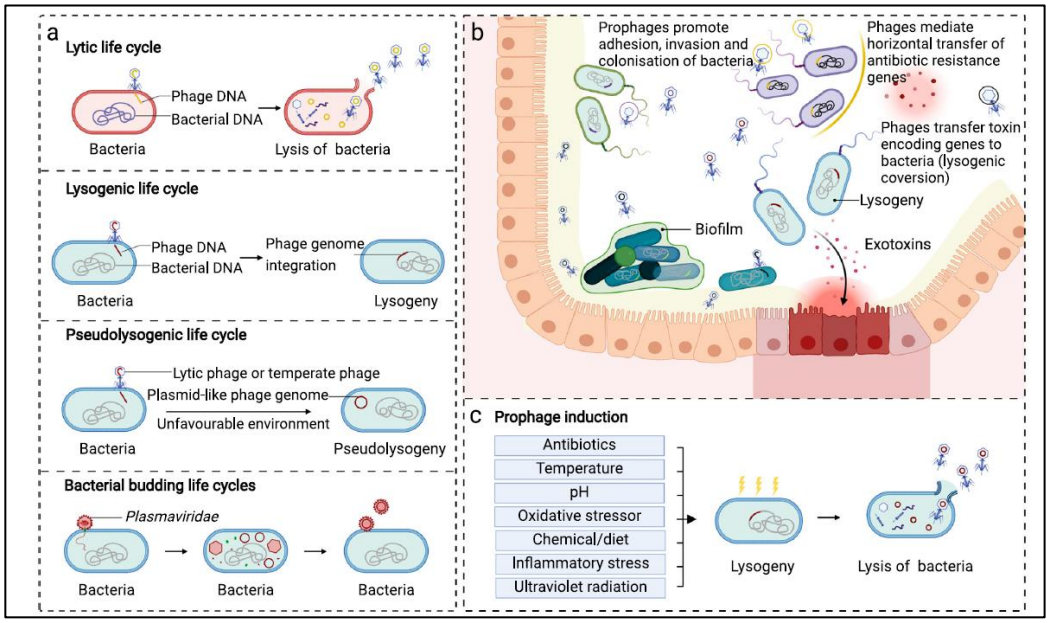

Figure 2: Interactions between bacteria and intestinal viruses. The existence of phages contains four main replicative patterns as part of their life cycle. The bacterial host experiences phenotype alterations after phage infection occurs. Bacteria naturally e

Interactions between the Gut Virome and Host Immunity

The GI mucosa contains large quantities of viruses and phages, which control both the innate and adaptive immune systems, as well as the intestinal lumen and feces. Immunity of the host. This interaction significantly influences host immunity [66]. The documented observations reveal that phages possess Ig-like domains in their viral capsid structures, facilitating their binding to mucin glycoproteins. One such phage carrying these domains is T4. Particular Ig-like proteins connect with glycan molecules displayed on the host's mucosal layer [67]. These prevalent, adherent phages on mucosal surfaces offer an antibacterial frontline of defense against luminal bacterial pathogens, which can aid in the development of an innate immune barrier [68]. Hoc proteins [Ig-like domain] on the mucosal surface of weakly adhering T4 phages exhibit aberrant subdiffusive motion behavior, which effectively reduces bacterial infections in human mucosal and epithelial cells [69]. Phages can work in conjunction with the human immune system to maintain immunological homeostasis, in addition to providing direct protection against bacterial invasion at the mucin layer and influencing the course of the illness [70]. Most phages in circulation are the mononuclear phagocyte system, after which they undergo filtering actions to extract them [71]. The liver and spleen serve as locations where phages are trapped for antibody destruction to occur within a 24-hour periodphage-specific antibodies within 24 hours [72] fig [3]. Numerous investigations have demonstrated that phages affect the human immune system by controlling cytokine release, improving opsonization, and identifying microorganisms, as

well as regulating T and B cell activity [73]. The treatment of germ-free mice with E. coli and T4 phages leads to increased infiltration of cells that produce interferon gamma [IFN-γ], according to a recent research study [74]. A significant portion of defensive T lymphocytes exists within the gut mucosa as CD4+ and CD8+ T cells. Research shows that E. coli phages increase colitis severity in mice with dextran sodium sulfate [DSS]-induced IBD through TLR9 and IFN-γ dependent pathways [75]. According to this research, phages are likely to be viable therapeutic targets and are involved in the pathophysiology of IBD [76]. Host immunity, along with the maintenance of gut homeostasis, requires eukaryotic viral colonization within the gut [77]. Bulk intestinal virus recognition using surface receptors, IFN-β is produced by TLR3 or TLR7, which shields the body against inflammation [78]. The cytosolic viral RNA detector RIGI activates interleukin-15 [IL-15] synthesis, which supports homeostasis of intraepithelial lymphocytes [79]. The immune response triggered by murine norovirus colonization in mice protected intraepithelial lymphocyte homeostasis and was coupled with vital defense mechanisms against Citrobacter rodentium infection [80]. Murine astrovirus [MAV] protection of immunocompromised mice occurred through its IFN-γ production [81]. Studies confirmed transmissibility by transferring feces between animals and allowing them to live together. According to these lines of evidence, eukaryotic viruses in the gut regulate host homeostasis by coordinating human immunity and bacterial activity .Studying the interconnected activities between bacteria and viruses with human hosts continues to gain substantial growth [82].

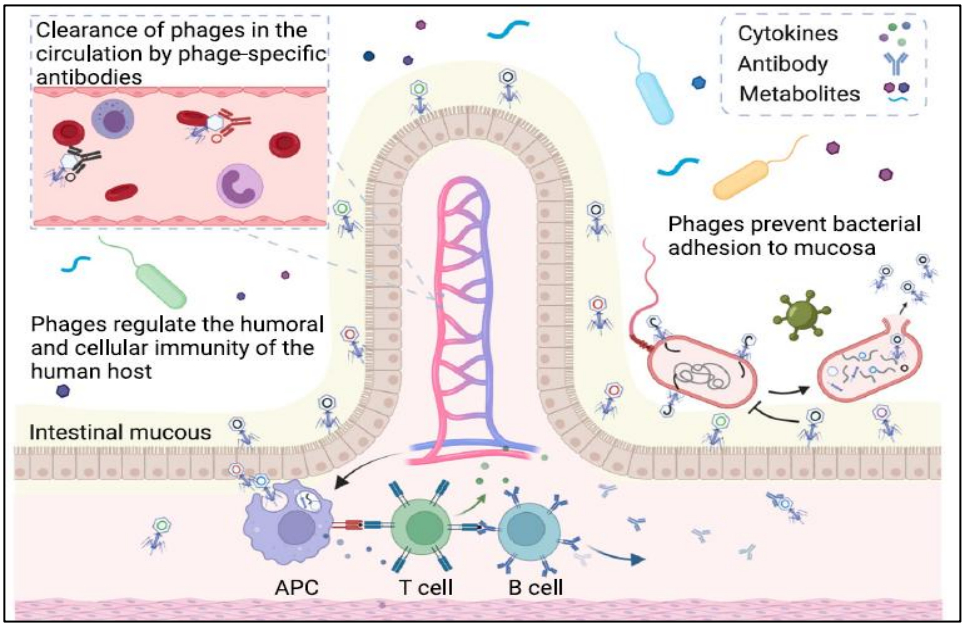

Figure 3: Gut virome and host immunity: the relationship between the human immune system and phages. The preservation of immune responses and gut homeostasis is dependent on eukaryotic viruses. The adherence of phages to human GI tract mucosal surfaces prevent

New scientific findings suggest that viruses residing in human body fluids may influence drug metabolism and absorption through either direct or indirect microbial pathways [84]. Scientists are now exploring bacteriophage applications as therapeutic agents to perform three key immune system functions: transporting genes that regulate immunity, modifying the microbiome before vaccinations, and assisting with the training of immune systems in the context of persistent infections [85].

Conclusion

The gut virome is a significant aspect of human health that impacts the immune system, microbial homeostasis, and predisposition to chronic disease. Although the available information is still sparse, the relationship between bacteriophages and eukaryotic viruses, as well as between the microbiome and host immunity, is currently being researched extensively. Future research should be devoted to standardized virome profiling, the integration of virome analysis with clinical diagnostics, and the development of new phage-based therapeutic strategies. Sealing these gaps, the gut virome would become the foundation of precision medicine and new therapies.

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