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HOST–MICROBIOME AND PHAGE INTERACTIONS IN HEALTH AND DISEASE: MECHANISTIC INSIGHTS AND THERAPEUTIC IMPLICATIONS

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Abstract

The human microbiome is a dynamic ecosystem, which has been found to combine microbial metabolism, immune regulation, and epithelial barrier functions to keep the host in a state of homeostasis. Disease related dysbiosis is increasingly being shown to be not merely a change in bacterial composition but a breakdown of the regulation of microbial ecosystems. At the heart of this regulation is the phageome that prevails in the gut virome and actively influences the dynamics of bacterial populations, functional capability and gene exchange. In this review, existing knowledge of mechanistic insights on host-microbiome and microbiome-phage interaction is synthesized, with focus on roles of microbial metabolites, immune sensing signals, and phage mediated ecology processes in shaping health and disease. We explain how disruptions of bacterial-phage interactions cause chronic inflammation, metabolic and immune pathology and therapy responses, and how the main methodological and conceptual problems restrict the current phageome studies. Incorporation of phage biology into microbiome models is vital to the future of ecosystem-based disease models, as well as to establish specific microbiome- and virome-directed treatments.

Keywords: Microbiome, Phageome, Host-microbe interactions, Gut immunity, Dysbiosis, Microbial metabolites, Bacteriophages, Chronic disease.

1. INTRODUCTION

The human microbiome is an integrated ecosystem that regulates the host's metabolism, immunity, and barrier integrity through synergistic interactions among microbes and viruses. Many chronic inflammatory and metabolic diseases arise from disruptions of these regulatory networks rather than from mere microbial

imbalance. Metagenomic studies have shown that the gut virome is composed primarily of non-eukaryotic viruses, with bacteriophages accounting for about 97.7% of total viral sequences, and eukaryotic and archaeal viruses comprising 2.1% and 0.1%, respectively (Zhang and Wang, 2023). These results have taken the conceptualization of the gastrointestinal microbiome beyond a list of bacterial species and established it as a dynamic ecosystem that has interacted with other interkingdom over long-term interactions based on predation, horizontal gene transfer, and lysogeny. The identification of crAssphage by re-examination of fecal viral metagenomes in 2014 has been an example of how mechanistic understanding of gut viral ecology has been motivated by metagenomics (Ullah et al., 2023). Later analyses found broad genomic diversity among crAss-like phages, with 249 distinct genomes identified from 702 human fecal samples, and showed subdivision into numerous subfamilies and candidate genera, consistent with an evolutionarily successful gut phage lineage (Smith et al., 2023).

At the initial stages of life formation, it was proven that the phageome also exists simultaneously with the colonization of the intestines by bacteria. The infant intestinal phageome may have an endogenous origin, arising from prophages carried by initial colonizing bacteria. Subsequently, the infant and maternal gut communities share crAss-like viruses as Bacteroides is rapidly spreading (Shamash and Maurice, 2022). Moreover, the phageome cannot be influenced solely by bacterial populations; instead, it displays features linked to changes in ecological/abiotic stability and inflammatory mechanisms. Also emerging is the mechanistic understanding of how the immune system perceives our viromes, as reported in studies of a near tenfold increase in phage abundance in tissue samples from Crohn's disease, accompanied by changes in phage morphotypes and a shift in the distribution of temperate and virulent phages between the ulcerated and non-ulcerated mucosa (Federici et al., 2021). Also becoming apparent is the mechanistic understanding of our viromes through studies of murine (mouse) colitis in women

and the association of TLR3 (toll-like receptor 3) and TLR7 (toll-like receptor 7). The presence of host pattern recognition receptors indicates that the immune system can sense viral signals in the intestinal milieu (Nabi-Afjadi et al., 2023). This review focuses on host–microbiome–phage interactions as mechanistic drivers of health and disease, moving beyond descriptive inventories toward causal frameworks: how phage predation and lysogeny reshape microbial community structure; how phage-driven gene exchange and selection pressures influence bacterial function; and how phage–host immune interfaces (including mucosal exposure and innate viral sensing pathways) contribute to inflammatory tone and tissue homeostasis. By integrating ecological, molecular, and immunological perspectives, we aim to clarify why the phageome should be treated as an integral regulatory component of the microbiome, and how this understanding can inform therapeutic implications (e.g., rational microbiome modulation, virome-aware interventions, and phage-based strategies) in complex chronic diseases.

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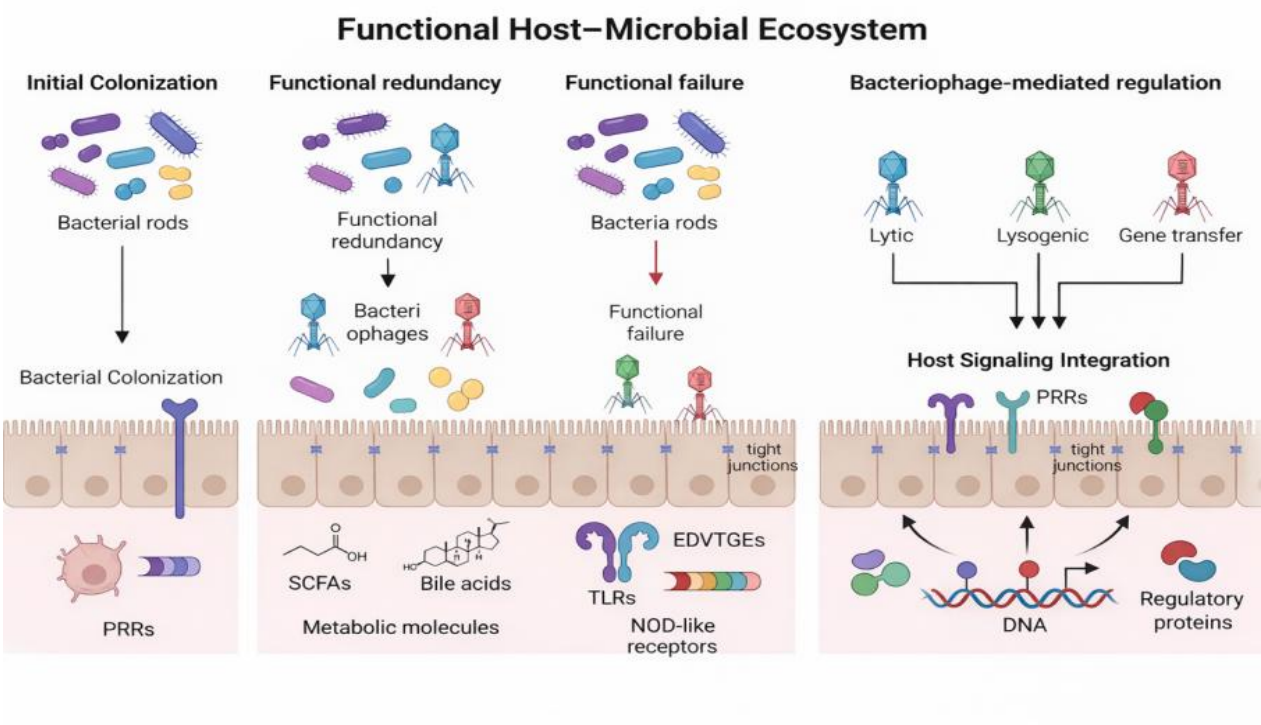

Figure 1. Ecosystem functional-ecological model of human host-microbiome-phage. Microbial communities are outlined to be functionally organised systems affected by ecological communications, host regulatory signalling, and bacteriophage control. Perturbations may lead to functional recovery and homeostasis, or to a dysbiosis state, an alternative stable state. It emphasizes the conserved functional capacity rather than taxonomic composition. It adds the phageome as a vital level of control under the perspectives of ecosystem stability and disease susceptibility (Adopted from Flores et al., 2025).

2. Functional Organization of the Human Microbiome

Human microbiome can best be viewed as a functionally structured ecosystem where host-relevant effects arise due to (i) metabolic capacity shared across different taxa, (ii) interconnected metabolic networks that allow cross-feeding and sharing of resources, and (iii) only a limited number of keystone organisms and metabolites that have disproportionate impact on barrier integrity, immune tone, and stability of the ecosystem. This functional organization supports the production of a convergent host phenotype by distinct microbial communities with significant taxonomic differences.

2.1 System and stability of an ecosystem

Despite the significant differences in the taxonomic composition of the gut microbiome among healthy people, the functional capacity of the microbiome is highly conserved across populations. The metabolism of carbohydrates and amino acids (Durack and Lynch, 2019), fermentation, and oxidative phosphorylation are core metabolic pathways that are always present and help demonstrate the concept of functional redundancy. Such redundancy facilitates the production of similar metabolic products by related microbial groups, such as short-chain fatty acids, vitamins, and secondary bile acids (Khalil et al., 2024).

The functional range of the gut microbiome is vast at the genomic scale, with 9.9 million unique microbial genes observed in healthy individuals from several continents. This genetic reservoir forms the basis of the ability of microbial communities to sustain metabolic output when there are changes in composition (Goodrich et al., 2017). Community structure can thus change with time without altering fundamental processes until large-scale perturbations (e.g., exposure to antibiotics, persistent dietary changes, or inflammation) erode the buffering ability and disrupt ecosystem performance. The loss of functional redundancy is thus one of the characteristic attributes of dysbiosis, whereby community instability is connected to impaired metabolism and host vulnerability (Durack and Lynch, 2019).

2.2 Metabolite networks and cross-feeding of microbes.

Microbial activities in the gut are structured into mutually reliant metabolic networks, but not solitary. Dietary substrates are metabolized in a series of sequential, cooperative processes in the colon, during which other members of the community use intermediate metabolites. Cross-feeding interactions are one of the central organizing principles of this networked metabolism, enabling efficiency and stability to prevail even in changing environmental conditions (Shetty et al., 2022). An example in point is that of acetate-dependent metabolism, which is well-characterized. Some butyrate-generating taxa, such as *Faecalibacterium prausnitzii*, are acetate co-factor growth signals and

cannot be grown in isolation. These dependencies form higher-order metabolic networks that include individual taxa, demonstrating how the destabilization of individual metabolic connections may be propagated throughout the ecosystem, even in the absence of apparent taxonomic collapse (Onodera et al., 2025).

2.3 Disproportionate functional drivers in keystone taxa.

In this distributed ecosystem, there is a group of taxa of microorganisms that acts as a keystone species, and their effects are greater than their relative abundance. These organisms are essential for maintaining the integrity of epithelial barriers, supporting the immune response, and producing metabolites important to host physiology (Safarchi et al., 2025). Indicatively, *Akkermansia muciniphila* (Mo, et al., 2024), can help maintain the gut barrier by inhibiting antigen translocation and alleviating inflammation-related permeability, especially in the ageing group. In the same vein, the short-chain fatty acid production is pegged on major butyrate-producing taxa, which are *Faecalibacterium prausnitzii* (Effendi, et al., 2022), *Roseburia intestinalis*, and *Anaerostipes butyraticus* (Wu et al., 2021). These taxa contribute to host- microbiome interactions by stabilizing the interactions between epithelial and immune cells through their metabolic activity, supporting epithelial energy requirements, and regulating the immune cell activity. Due to these functions, these organisms are commonly referred to as functional anchors, and their loss causes disproportionate destabilization of the ecosystem (Pathak and Banerjee, 2024).

2.4 Metabolites of microbes as host-active effectors.

Microbial effects on host physiology are also achieved, mediated mainly by bioactive metabolites, which interconnect microbial metabolism with epithelial, immune, and systemic signaling. Colonial fermentation is a form of carbohydrate metabolism that facilitates barrier maintenance and immune homeostasis. Conversely, the scarcity of fiber promotes a transition towards protein fermentation, which is accompanied by the accumulation of metabolites that can impair epithelial function and lead to

inflammation. Food content has thus been shown to be an imposing upstream controller of microbial metabolic products and downstream host signals (Ullah et al., 2024).

Short-chain fatty acids (SCFA) are short, unpolymerized organic compounds that readily break down into individual gases. Short-chain fatty acids (SCFA) Short-chain fatty acids (SCFA) are short, un-polymerized molecules, which can be turned into individual gases easily. In large amounts, the short-chain fatty acids (SCFAs) are obtained through fermentation of dietary fiber by microorganisms, whose overall daily production ranges between 500 and 600 mmol (based on the availability of substrates). The commonest SCFAs are acetate, propionate, and butyrate, and their molar ratios can vary between 3:1:1 and 10:2:1 (Fusco et al., 2024).

SCFAs have both local and systemic actions. Butyrate is a primary source of energy to colonocytes and regulates gene expression via the inhibition of histone deacetylase, which participates in the anti-inflammatory and anti-neoplastic mechanisms. Propionate helps maintain epithelial energy metabolism and hepatic gluconeogenesis, and acetate is involved in lipid metabolism and cross-feeding relationships between microbes. Acetate and butyrate stimulate the secretion of mucin and augment the expression of the mucosal components of the barrier, like the MUC2, which strengthens the protective effect of the epithelia. The aggregate impact of all these actions is that SCFAs act as central integrators of microbial metabolism, barrier biology, and immunoregulation (Lange et al., 2023). Microbial metabolites are essential intermediates of communication between the microbiome and the host immune system. On the local level, they affect enterocytes and immune cells of the lamina propria; on the systemic level, they enter the circulation and regulate immune responses at remote sites. These channels enable microbial metabolic products to support nutrient processing and immune tuning, facilitating homeostasis and limiting the proliferation of opportunistic pathogens (Wiertsema et al., 2021).

3. Molecular Crosstalk Between Host and Microbiome

3.1 Pattern Recognition and Immune Signaling

The interaction between the host and the microbiome is triggered by an innate immune response to microbial-associated molecular patterns (MAMPs). Pattern recognition receptors (PRRs) are highly expressed in the intestinal epithelial cells (IECs) and antigen-presenting cells (APCs), such as macrophages and dendritic cells (DCs), in the intestine, especially on Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD-like) receptors (Abraham and Medzhitov, 2011). These receptors sense conserved microbial elements of both commensal and pathogenic microorganisms and signal these signals to intracellular pathways that comprise adaptor proteins, kinases, and transcription factors that control the expression of immune genes.

PRR signaling provides a fundamental defense against infection while limiting excessive inflammation. Commensal-derived MAMPs, when used as basal stimulants of epithelial PRRs, can maintain homeostatic processes, such as mucin secretion, antimicrobial peptide production, and cytokine induction (IL-18 and IL-22) (Chen et al., 2025). The production of IL-22, mainly by ILC3s and Th17 cells, is key to epithelial regeneration, tight junction regulation, and antimicrobial protection. Conversely, PRR activation during barrier disruption and tissue damage triggers inflammatory signaling, leading to the synthesis of cytokines, including IL-1, TNF-α, and IL-6, and to the attraction of innate and adaptive immune cells. Intestinal homeostasis maintenance also relies on regulatory pathways that are characterized by regulatory T cells (Tregs) and anti-inflammatory cytokines like IL-10 and TGF-β, which induce tolerance against commensal microbiota and prevent excessive tissue damage (Domingues and Hepworth, 2020).

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Table 1. Functional Pathways of Host-Microbiome-Phage Interactions and Biological Implications.

Functional domain	Key microbial / phage-derived factors	Primary host targets / pathways	Physiological roles in homeostasis	Implications for disease when dysregulated
Short-chain fatty acid (SCFA) metabolism	Butyrate, acetate, propionate	GPCRs (GPR41/43), HDAC inhibition	Maintenance of epithelial barrier integrity, immune tolerance, energy metabolism	Barrier dysfunction, chronic inflammation, metabolic disorders
Bile acid transformation	Secondary bile acids (e.g., deoxycholic acid)	FXR, TGR5 signaling pathways	Regulation of lipid and glucose metabolism, modulation of inflammatory tone	NAFLD, insulin resistance, metabolic syndrome
Tryptophan metabolism	Indole derivatives, AhR ligands	Aryl hydrocarbon receptor (AhR), immune cells	Mucosal immune homeostasis, epithelial protection, neuroimmune signaling	Inflammatory bowel disease, neuroimmune dysregulation
Microbe-associated molecular patterns (MAMPs)	LPS, peptidoglycan, flagellin	TLRs, NOD-like receptors, NF-κB/MAPK pathways	Immune maturation, controlled inflammatory signaling	Chronic inflammation, autoimmune and metabolic diseases
Extracellular vesicle signaling	Bacterial membrane vesicles	Cytokine signaling, epithelial and immune cells	Intercellular communication, immune modulation	Dysregulated immune responses, altered host signaling
Phage-mediated bacterial predation	Lytic bacteriophages	Bacterial population dynamics	Control of bacterial overgrowth, maintenance of community diversity	Loss of beneficial taxa, microbial instability
Lysogenic conversion	Prophage-encoded genes	Bacterial metabolic and stress-response pathways	Functional adaptation without taxonomic change	Enhanced virulence, altered microbial function

Functional domain	Key microbial / phage-derived factors	Primary host targets / pathways	Physiological roles in homeostasis	Implications for disease when dysregulated
Horizontal gene transfer	Phage-mediated gene exchange	Bacterial metabolic and resistance traits	Functional redundancy and ecosystem resilience	Antibiotic resistance, persistent dysbiosis

3.2 Microbial Metabolites as Signaling Molecules

A large group of signaling intermediates that mediate microbiome-host tissue crosstalk are microbial metabolites. The three main categories of metabolites have repeatedly been involved in immune and metabolic regulation, namely short-chain fatty acids (SCFAs), indole metabolites derived from tryptophan, and microbially modified secondary bile acids, as described in the previous section (Section 2). The most common fermentation products of microbes in the colon are SCFAs, mainly acetate, propionate, and butyrate, though acetate and propionate are usually present at high levels. Colonic epithelial cells preferentially use butyrate as an energy source, which is one reason it has a lower luminal concentration than acetate (Yang and Cong, 2021). In addition to their metabolic functions, SCFAs also act as signaling molecules through G protein-coupled receptor cascades and histone deacetylation via histone deacetylase (HDAC) inhibition, especially with butyrate. These pathways by which SCFAs act to modulate inflammatory signals, control access of immune cells to cytokine networks, including TNF-α, and facilitate mucus layer development through a variety of intestinal epithelial cell signaling pathways. Complementary mechanisms also play the role of enhancing immune tolerance, facilitated by SCFAs that promote the development of regulatory T cells (Treg). These involve direct induction of Treg differentiation through HDAC inhibition and GPCR-mediated pathways that enhance production of IL-10 and TGF-β, and indirect regulation of the dendritic cell to assume a tolerogenic phenotype that supports Treg proliferation (Xu et al., 2025).

Another metabolite-mediated immune and epithelial axis of metabolism is tryptophan metabolism. Indole products produced by microorganisms are ligands of the aryl hydrocarbon receptor (AhR), the activation of which triggers a translocation to the nucleus and regulates transcriptional programs related to immune regulation and maintenance of barricades (Coretti et al., 2025). A decrease in the production of AhR-binding ligands has been linked to metabolic impairment, and the reinstatement of AhR-binding ligand-producing microbial taxa has been shown to enhance epithelial barrier integrity and suppress hepatic steatosis. Mechanistically, the indole derivatives, indole-3-ethanol, indole-3-pyruvate, and indole-3-aldehyde increase epithelial integrity by acting on the apical junctional complex components, including Myosin IIA and Ezrin (Pan et al., 2025).

3.3 Microbiome-Mediated Epigenetic and Transcriptional Regulation

An epigenetic mechanism of microbiome-mediated metabolite signaling is the epigenetic regulation of host gene expression, such as histone modifications and dynamic alterations of DNA regulatory programs. These processes have the potential to support sustained changes in host transcriptional responses beyond the immediate receptor-mediated signaling (D'Aquila et al., 2020). It is considered one of the most well-defined pathways in which histone modification can occur, achieved by inhibiting histone deacetylases (HDACs) with microbial metabolites, specifically short-chain fatty acids (SCFAs). Histone acetylation is a reversible process that modulates chromatin accessibility and transcriptional activity. A rise in histone acetylation usually correlates with active gene expression, and a decrease with transcriptional suppression. As noted above, high levels of SCFA, predominantly butyrate, inhibit HDAC activity, thereby favoring transcriptionally permissive chromatin (Cai et al., 2025). Histone modification via the microbiome is mediated by regulating the activity of histone-modifying enzymes and the availability of metabolic substrates essential to their function. The SCFAs cover most of the currently reported microbiome-mediated histone modifications but are presumably merely a single part of a larger epigenetic

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regulatory system. Butyrate is the most widely investigated SCFA HDAC inhibitor. It has been reported to have anti-inflammatory properties by inhibiting the nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription (STAT) signaling pathways. Moreover, butyrate increases histone H3 acetylation of the Foxp3 locus and the differentiation and maintenance of regulatory T cells (Duan et al., 2023).

There is another sphere of transcriptional regulation involving non-coding RNAs (ncRNAs), indicating coordinated regulatory relationships between the microbiota and the host. Non-coding RNAs occur in eukaryotes and prokaryotes as well, and they are involved in the regulation of gene expression in a variety of biological situations. Host microRNAs may change during inflammatory reactions and then regulate epithelial and immune pathways, such as cytokine production and the generation of inflammatory signals. On the other hand, bacteria have been demonstrated to take up host-derived microRNAs, which in turn affect bacterial gene transcription and replication, thus indicating a bidirectional, cross-kingdom pathway to gene regulation (Qin and Wade, 2018).

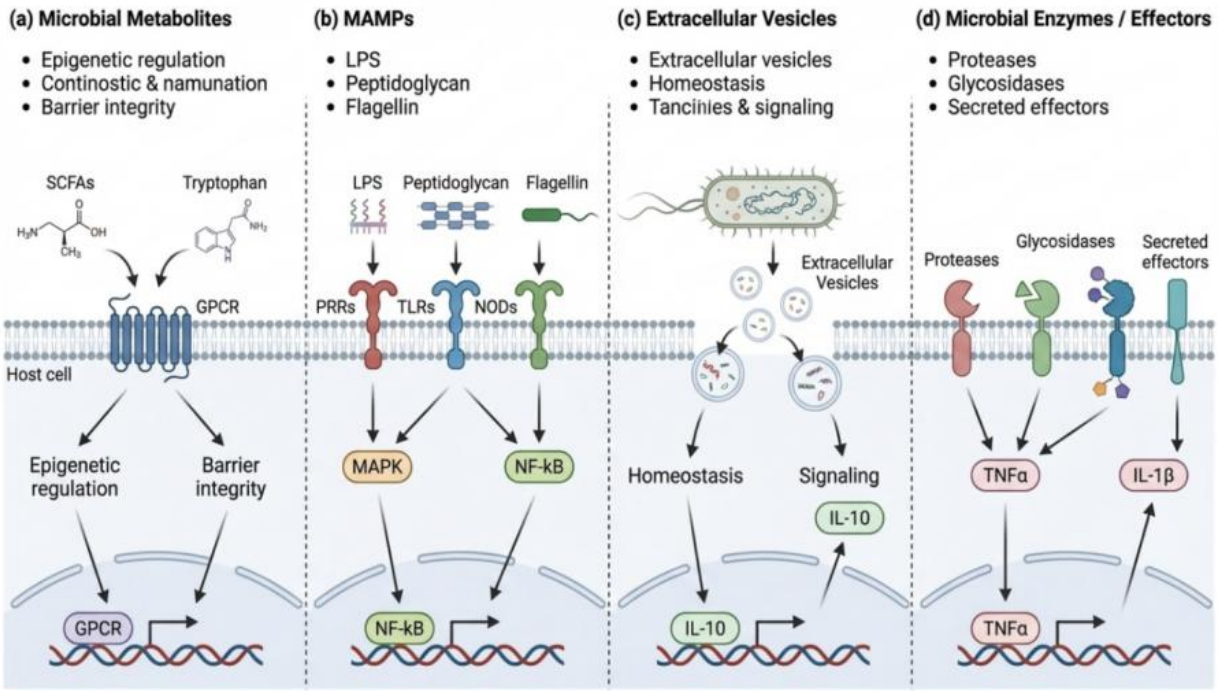

Figure 2. Crosstalk of the host and the human microbiome via common functional pathways. Microbial communities can relay messages to host tissues through a wide range of mechanisms, rather than on taxonomic identity per se. Signal: Microbial metabolite (e.g., short-chain fatty acids, tryptophan-derived products, polyamines) may use host receptors (e.g., GPCRs) to signal immune modulation, epithelial barrier function, and epigenetic programs. (b) Pattern recognition receptors (PRRs) (e.g., TLRs and NOD-like receptors) sense microbe-associated molecular patterns (MAMPs) (e.g., lipopolysaccharide, peptidoglycan, and flagellin) and trigger intracellular signaling pathways, which coordinate inflammatory and immune defense responses (NF-KB and MAPK). (c) Bioactive molecules: Microbial extracellular vesicles are delivery systems that interact with hosts to communicate, maintain immune homeostasis, and support gut-brain signaling. (d) Microbial enzymes, as well as the effectors they secrete, adjust host physiology by directing immune responses, cellular survival mechanisms, and the inflammatory tone (Adopted from Sanam et al., 2026).

4. Human Phageome the Microbiome Integral Element.

Scientists are increasingly recognizing that the human microbiome is an ecosystem and that a significant number of viruses (primarily bacteriophages) are a vital, often unappreciated component of it. Bacteriophages, collectively referred to as the human phageome, are more abundant than their hosts in most regions of the human body; they may significantly impact the functionality of the microbiome and its guardians, the human immune system, as well as an individual's predisposition to disease (Godsil et al., 2025). The metagenomic sequencing methods have proven that although the previous perception of bacteriophages was that they passively co-exist with other microorganisms in a gut or any other area of a host, recent studies have indicated that, in fact, a human phageome is a very significant and actively functional element of a human microbiome rather than an incidental addition or by-product (Ranveer et al., 2024).

4.1 Diversity and Distribution of Bacteriophages in the Human Body

Bacteriophages are present in most human-related micro-ecosystems, such as the gastrointestinal tract, oral cavity, skin, and respiratory tract, where they constitute host-specific viral communities that are conditioned by local environmental factors and the microbial community. The gastrointestinal tract has the highest phage diversity and abundance. Quantitative studies have approximated human stool to harbor about 10^{9} - $10\ 1^{0}$ particles of the virus-like particles per gram, out of which about 97 -98% are bacteriophages. Most gut phageomes are dominated by double-stranded DNA phages, with the majority belonging to families traditionally viewed as part of the Caudovirales (such as *Siphoviridae, Myoviridae*, and *Podoviridae*) (Lee et al., 2024). There is also a presence of single-stranded DNA phages belonging to the Microviridae family, and crAss-like phages are among the most numerically dominant viral groups in the gastrointestinal tract, hypothesized to infect Bacteroides species, which form the majority of the microbiota in adults. Phage populations are also abundant in the mouth cavity, where phages intrude into dominant bacterial genera, including *Streptococcus, Actinomyces, Veillonella*, and *Prevotella,* which contribute to biofilm assembly and microbial turnover. Conversely, skin-associated phageomes are highly site-specific, with phages adapted to local physicochemical environments, such as pH, moisture, and lipid levels, and are typically specific to *Staphylococcus, Corynebacterium*, and *Cutibacterium species* (Shkoporov et al., 2019). Despite the respiratory tract usually showing lower microbial diversity, phages of *Streptococcus, Pseudomonas*, and *Haemophilus* are consistently observed. Phage lifestyles also help to increase niche diversity. In the adult gut ecology, temperate phages are most common (Nolan and Hill, 2019). Still, lytic phages are more common in early life or during ecological instability, such as exposure to antibiotics or inflammation, highlighting the dynamic nature of phage populations throughout the human lifespan (Tzani-Tzanopoulou et al., 2021).

4.2 Phage–Bacteria Dynamics

Phage-bacteria interactions are an essential ecological force that determines the structure and the functioning of the microbial community. Lytic infection allows bacteriophages to control bacterial population density through predator-prey interactions, selectively limiting the dominant taxa and enhancing community diversity. This density-dependent control helps contain bacterial overgrowth and stabilize the microbial ecosystem. Simultaneously, temperate phages become part of bacterial genomes as prophages, enabling lysogenic conversion and allowing adaptation of functions without immediate lysis of the host cell (Castledine and Buckling, 2024). In the process, prophage-encoded genes may regulate bacterial metabolism, stress responses, and virulence-related traits, thereby contributing to the phenotypic diversity of microbial communities. The Bacteriophages also take the center stage in horizontal gene transfer, in which genetic material is exchanged between bacterial populations. This gene flow promotes microbial diversification, functional redundancy, and resilience to ecological change, and also facilitates rapid community reorganization under selection pressure (Jdeed et al., 2025).

4.3 Phagesphere Host Immune Interactions.

Besides direct contact with bacteria, bacteriophages also interact with the host immune system, especially at mucosal surfaces, where immune surveillance is most active. Several reports have shown that phages can penetrate the mucus layer and the epithelial barrier, and that phage particles have been identified in systemic structures such as the blood and lymphoid tissues, indicating that phage-host interactions are not limited to the gut lumen. Phage capsids often have immunoglobulin-like glycoprotein binding domains, which result in phage enrichment in the mucus layer. Such localization enhances the likelihood of bacterial lysis at the epithelial interface and decreases overproduction of the host immune response, which is part of barrier protection. Mutations in phageome structure have been linked to inflammatory diseases, with the most recent being inflammatory bowel disease, where changes in phage numbers and distribution are associated with mucosal inflammation (Zalewska-Piątek, 2023). These

findings indicate that phageome dysbiosis may contribute to immune dysregulation, affecting both microbial ecology and host immune signaling.

5. Microbiome–Phage Interactions in Health Maintenance

Bacteriophages are vital for stabilizing microbiomes and, in turn, host health. In healthy people, resident phages have many beneficial effects on commensal bacteria, supporting microbial, immune, and barrier homeostasis. Phages not only act as predators to bacteria but also regulate community structure, adjust the bacterial gene pool, and indirectly impact host immune responses, and are thus described as being intrinsic regulators of microbiome homeostasis (Keen, and Dantas, G. (2018).

5.1 Phage-Mediated Pathogenic Bacteria Control.

The mechanism of targeted control of potentially pathogenic bacteria and preservation of useful commensal populations results from selective pressure exerted by bacteriophages on bacterial populations: strain-specific infection and lysis. Metagenomic and experimental studies show that lytic phages inhibit the growth of opportunistic pathogens, including Escherichia coli, Clostridioides difficile, Enterococcus faecalis, and Klebsiella pneumoniae, in the gastrointestinal tract. In healthy ecosystems, phages specifically attack rapidly growing bacterial populations, thereby restraining the dominance of pathogens and maintaining a balance among microbes. Moreover, the prophages integrated into commensal bacterial genomes confer a competitive advantage by exerting control over further colonization by pathogenic strains through superinfection exclusion, a phenomenon also triggered by prophage integration (Niazi, 2025).

5.2 Maintenance of Microbial Diversity

Phages also help maintain bacterial diversity by influencing the structure and organization of microbial communities at the species and strain levels. The relationship between phages and bacteria can be viewed as a predator-prey relationship, where the

ecological theory of kill-the-winner favors coexistence and avoidance of competitive exclusion. Longitudinal analyses have shown that the phage and bacterial communities in healthy adults do not change over time, i.e., are stable over long periods. That phage composition is consistently well matched to bacterial host specificities. During persistent interactions, phages can increase ecosystem stability to environmental changes, including dietary variability, temporary infections, and temporary stressors. Horizontal gene transfer, partially through phage-mediated transduction, also promotes microbial adaptability by spreading genes for nutrient metabolism and niche differentiation, leading to long-term microbiome stability (Alkhalil, 2023).

5.3. Stabilization of Host Immune Responses.

Bacteriophages play a role in maintaining immune homeostasis, both indirectly by influencing the composition of bacterial communities and directly by acting on host tissues. Phages regulate immune pathways by modulating bacterial antigen exposure and metabolic outputs without causing excessive inflammation. The Phages have also been observed to interact with epithelial cells and immune cell populations such as macrophages and lymphocytes, facilitating immune tolerance and optimal immune surveillance. Animal and human experiments have indicated that a stable and diverse phageome is linked to controlled inflammatory signalling and regulated activation of innate and adaptive immunity, in part through microbiota-derived metabolites.

5.4. Effect on the Mucosal Barrier Integrity.

A primary interface of microbiome and host immunity is the intestinal mucosal barrier, which is maintained by phages. Phages accumulate in the mucus lining, creating an additional antimicrobial barrier that prevents bacterial attachment to the epithelial surface. The phages indirectly preserve the integrity of the barrier by repressing bacteria that degrade mucus or release pro-inflammatory factors. Moreover, short-chain fatty acids, produced under phage-mediated regulation of commensal bacteria, support energy production in epithelial cells and in mucus (Cianci et al., 2025).

6. Dysbiosis as a Mechanistic Driver of Disease

The dysbiosis (disturbance of the gut microbiome) is more than a simple correlation with numerous diseases, as a growing body of research has established. It is likewise one of the leading causes of multiple diseases by at least three (3) pathways: total desaturation of epithelial barrier integrity; induction of metabolic endotoxemia; and dysregulation of neuroimmune and neuroendocrine signaling pathways. All three (3) mechanisms are interconnected and lead to the development of systemic inflammation and multi-organ dysfunction through the metabolic, immune, or neurologic axes.

6.1 Dysfunction of Barrier and Microbial Translocation.

Heightened Intestinal Permeability.

The intestinal barrier is composed of various layers, including mucus, epithelial tight junctions, immune components, and the gut-vascular interface. Dysbiosis alters microbiota composition, reduces the synthesis of valuable products, and impairs the integrity of tight junction proteins in the epithelium, including occludin, claudins, and zonulin, thereby disrupting the intestinal barrier. The experimental and clinically based research reinforced the idea that dysbiosis and intestinal permeability (also known as a leaky gut) are elevated, allowing bacterial components to enter the bloodstream (Cebi, M., & Yilmaz, Y. (2025). The tight junction protein expression was deeply reduced, the FITC-dextran permeability was higher, and the bacterial product circulation was raised in a few weeks after the change of diet in animal models of diet-induced dysbiosis induced by high-fat diets. All these abnormalities existed before the clear metabolic disease had occurred, and further supports the hypothesis that it is the dysregulation of the intestinal barrier that is causing the metabolic disease. Similar findings have been reported in human studies: people with dysbiosis have higher lactulose/mannitol ratios, further supporting the argument that the intestinal epithelium is not functioning effectively. Greater microbial diversity, and more specifically a reduction in the abundance of Short Chain Fatty Acid (SCFA)-producing taxa (e.g.,

Faecalibacterium and Roseburia), is also linked to poor maintenance of the mucus layer and poor regenerative mechanisms in damaged epithelia (DiMattia et al., 2024).

Systemic Inflammation

The change in location of bacteria parts (disrupted bacterial cellular constituent) through interference with the barrier functioning causes the translocation of bacterial products including lipopolysaccharides, peptidoglycans and DNA of bacteria into the blood circulation at the local (enteral) and site-specific (general) sites in the body through direct local action on TLR4, and/or NLR stimulation to trigger systemic (mild) inflammation. It has also been found that bacterial DNA and/or endotoxins are present in the blood circulation and in other tissues, such as adipose tissue, liver, and vascular systems, that cause both macrophage infiltration and release of inflammatory cytokines (TNF-α, IL-1β, IL-1 2- 6) and stimulation of the systemic inflammatory response system (Rosendo-Silva et al., 2023).

6.2 Metabolic Endotoxemia and Chronic Inflammation.

LPS-induced Immune Activation.

Metabolic endotoxemia is a state that occurs due to a chronic and chronically elevated level of circulating lipopolysaccharide (LPS) in the blood stream that is predominantly a result of Gram-negative intestinal bacteria but is commonly linked to a changed microbiome (or dysbiosis), whereby more abundant Proteobacteria and fewer of the bacteria which produce short-chain fatty acids (SCFA) result in the intestine releasing and absorbing more LPS through the damaged intestinal wall.LPS in the blood binds to *T. Even* small changes in plasma LPS levels can lead to the development of chronic inflammation, oxidative stress, and immune cell mobilization to metabolic tissues. Chronic exposure to low doses of LPS results in the major components of metabolic disease, including adipose tissue inflammation, fatty liver, and glucose insensitivity, indicating that this condition is a mechanistic causative agent of metabolic disease rather than a secondary effect in animal studies (Jian et al., 2025).

Insulin Resistance

The prolonged effects of LPS-induced inflammation affect insulin signaling pathways by serine phosphorylation of IRS and prevent glucose diffusion into tissues. The significant contribution of insulin resistance, not related to caloric intake or excess weight gain, is made by chronic LPS-dysbiosis (i.e., fermentation by a lysogeny-activated organism). The loss of SCFA, a key product of microbial fermentation, has also been proposed to make the condition of insulin resistance even worse, given the fact that SCFA stimulates insulin response by its ability to activate GPR41 and GPR43, stimulate GLP-1 and PYY secretion in the gut, and exert anti-inflammatory effects on the liver and fat (Ponce-Lopez, 2025).

6.3 Neuroimbalance and neuroendocrine disturbance.

Gut–Brain Axis

The Gut Microbiota is relevant in bi-directional communication between our gut and brain by various mechanisms (neural, immune, and endocrine). In case the gut microbiota becomes dysbiotic, this communication is disrupted by altering the nature of microbial metabolites, amplifying systemic inflammation and dysregulating both vagal and hormonal signalling. Once the barrier between the intestine and the central nervous system is damaged, microbial metabolites can enter the central nervous system via the bloodstream, in addition to their direct entry through the destruction of the blood-brain barrier (Chidambaram et al., 2022). The ensuing pathways of neuroinflammatory responses and microglial activation induced by these mechanisms are believed to cause cognitive and behavioural alterations related to dysbiosis. It has been experimentally shown that when we undergo inflammation driven by a dysbiotic gut microbiota, the hypothalamic-pituitary-adrenal (HPA) axis shows altered activity, leading to increased cortisol release and hyperreactivity to stress. Moreover, dysregulation of metabolism and the immune response as a result of dysbiosis is reinforced by a negative feedback loop driven by dysregulation of HPA axis activity

(Vaziri et al., 2025).

Microbial Neuromodulators

A variety of intestinal microbes can synthesize and regulate a range of neuromodulator metabolites, including short-chain fatty acids, tryptophan metabolites, GABA, serotonin precursors, and dopamine-related compounds. The concentrations of these neuromodulators may be influenced by changes or imbalances in the gut microbiome (dysbiosis), which can interfere with neurotransmitter signaling and the balance between the immune system and brain cells. Low concentrations of SCFA interfere with microglial activation and the regulation of the blood-brain barrier, but elevated concentrations of pro-inflammatory metabolites can also stimulate neuroinflammation. These dysbiosis-induced alterations in the gut microbiome structure are linked to numerous changes in mood, stress response, and cognitive function in both animals and humans (Mirzaei et al., 2021).

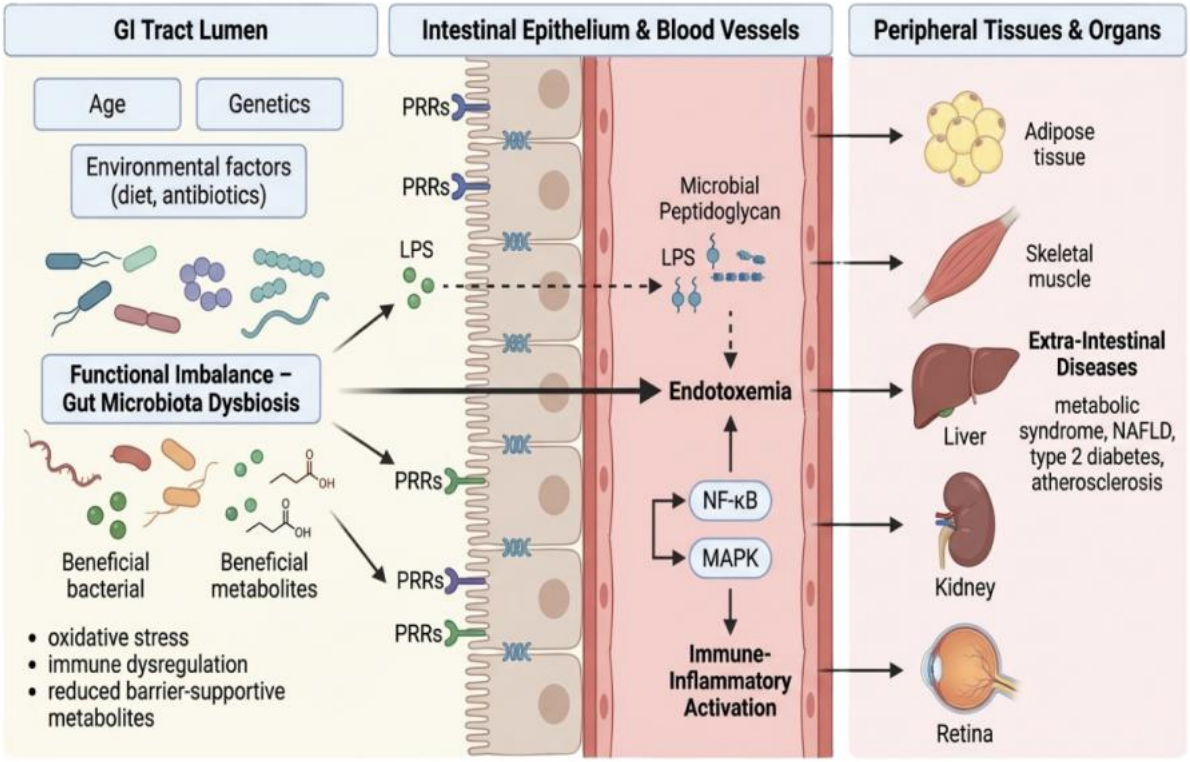

Figure 3. Mechanistic pathways linking gut microbiome dysbiosis to systemic disease.

Disruption of the gut microbiome's standard function, driven by host and environmental factors, leads to compromised epithelial barrier integrity and elevated intestinal permeability. Microbial-derived products, such as lipopolysaccharide and uremic toxins, are translocated and enhance endotoxemia and activation of innate immune and inflammatory signaling pathways. Such mechanisms play a role in persistent immune malfunction and metabolic inflammation, where gastrointestinal dysbiosis is associated with extra-intestinal disorders of peripheral tissues, including adipose tissue, liver, muscle, kidney, and retina (Adapted from Kumar et al., 2019).

7. Microbiome–Phage Contributions to Non-Communicable Diseases

Microbiome–Phage Interactions in Cancer

Cancer is the second leading cause of mortality worldwide and is increasingly recognized as a non-communicable disease influenced by host–microbiome interactions. Emerging evidence suggests that both the bacterial microbiome and the phageome contribute to cancer initiation, progression, and therapeutic response through complex ecological and immunological mechanisms. Dysbiosis of the gut and tissue-specific microbiota can promote carcinogenesis by inducing chronic inflammation, producing genotoxic metabolites, and altering host immune surveillance. Bacteriophages play a critical yet underexplored role in this process by shaping bacterial community composition through lytic and lysogenic cycles, thereby indirectly influencing carcinogenic or protective microbial functions (Bagheri et al., 2022).

Phages can modulate cancer risk by selectively targeting bacterial populations involved in pro-tumorigenic pathways, such as those producing secondary bile acids, reactive oxygen species, or inflammatory mediators. Conversely, prophage induction under conditions of stress (e.g., chemotherapy, oxidative stress, or inflammation) may enhance horizontal gene transfer, leading to the spread of virulence factors, toxin genes,

or antibiotic resistance among bacterial communities associated with tumors. Additionally, phage-encoded proteins and phage-derived nucleic acids have been shown to interact directly with the host immune system, influencing antigen presentation, cytokine signaling, and tumor-associated immune responses (Islam et al., 2023).

Recent studies have also highlighted the role of the phageome in shaping responses to cancer therapies, including immunotherapy and chemotherapy. Alterations in phage diversity and abundance have been correlated with treatment efficacy and adverse effects, suggesting that phages may serve as biomarkers for cancer prognosis or therapeutic outcomes.

(Kumar et al., 2022).

7.1 Metabolic Disorders

Obesity

Many metagenomic analyses of the gut microbiome demonstrate that obese individuals exhibit taxonomically and functionally dysregulated microbiomes, characterized by markedly different ratios of *Firmicutes* to *Bacteroidetes*, reduced microbial diversity, and distinct gene expression profiles. The intestinal microbiome of a fat individual is composed of numerous additional microbes that break down complex carbohydrates into energy, resulting in increased nutrient uptake and the development of obesity (Geng et al., 2022).

As the bacterial microbiome adapts to obesity, the gut virome, or viral community, varies. According to a detailed review of the virome, it becomes clear that when an individual becomes obese, the virome tends to be characterized by a reasonably high phage-diversity, and that phages infecting *Firmicutes* and *Proteobacteria* tend to increase in abundance as a result of the phage-driven selection pressure influencing bacterial dominance of the obese gut microbiome. The viruses may also participate more indirectly in bacterial metabolism as lysogenic conversion and/or horizontal gene

transfer agents. Animal research has shown that the microbiomes transplanted into the gut of obese donors share the same metabolic characteristics as the donors, including elevated fat deposition and insulin resistance (Borrego-Ruiz and Borrego, 2025).

Type 2 Diabetes

Research studies examining the occurrence of viruses that infect bacteria (bacteriophages) in patients with Type 2 diabetes (T2D) have shown that these patients exhibit distinct expression patterns of bacteriophages that infect bacteria that produce Short Chain Fatty Acids (SCFAs). This implies that the diminution of the bacteria that produce SCFAs, which is caused by the occurrence of these viruses, is one of the causes of metabolic issues linked to Type 2 Diabetes. Inflammation and oxidative stress may also amplify the lysis (cell death) of these specific bacterial species and stimulate the release of LPS by dead bacteria, further boosting the immune system and causing chronic inflammation related to T2D.

7.2 Autoimmune and Allergic Diseases

Autoimmune and allergic diseases are considered autoimmune-mediated disorders (Wang et al., 2015). A disease involving autoimmune mediators or allergies is referred to as an autoimmune disease (Wang et al., 2015).

IBD Inflammatory Bowel Disease (IBD)

Both Crohn disease and ulcerative colitis (UC) belong to the growing literature that is laden with the hypothesis that there is a drastic rise in the viromic diversity within the bowels of patients afflicted with IBD. Various strains of bacteria have been linked to reduced intestinal bacterial diversity due to increased abundance of bacteriophages, especially those in the Caudovirales family, and to the obliteration of the intestinal epithelial barrier. This is because the destruction of bacteria by bacteriophages reduces the stability of the microbial population in a particular area, thereby increasing exposure to bacterial antigens and eventually activating the mucosal immune system. Research on animal models suggests that the virome boosts intestinal inflammation,

even in the absence of apparent bacterial infection (Gong et al., 2016).

Asthma

Early disturbances in microbial composition are positively associated with asthma development. To be more precise, infants with low birth gut microbial diversity, as well as infant gut microbial maturation, are more vulnerable to contracting allergic airway disease (AAD). There is still a need to do further research. Still, the initial results point to the infant virome affecting immune education and creation of a healthy bacteriome and immune tolerance through the regulation of bacterial successions and T_H2 cell developmental signatures by modulating the T_H2 signaling pathways. It is also believed that phages may indirectly mediate asthma pathogenesis by regulating the establishment of specific immunomodulatory bacteria, which play a key role in inducing T-regulatory cells and a balanced TH2 immune response. Nevertheless, cursory studies have been conducted on the mechanisms by which phages regulate the bacteriome and their role in the overall progression of asthma (Abrahamsson et al., 2014).

Rheumatoid Arthritis

RA has been associated with intestinal microbiota dysbiosis, specifically the rise in *Prevotella spp.* and the decline in beneficial commensals. The phages can also regulate bacterial populations through bacteriophage-mediated modulation and alter the accessibility of antigens, thereby triggering molecular mimicry that leads to the development of autoimmune disease. Virome profiles have been reported to change in several autoimmune conditions, implicating bacteriophages in chronic immune stimulation via the continuous turnover of bacteria (and subsequent release of antigens) within the host immune system (Horta-Baas et al., 2017).

7.3 Neurological and Neuropsychiatric Disorders.

Depression

Depression is linked to an altered gut microbiota, increased intestinal permeability, and systemic inflammation. Changes in microbial metabolites associated with microbial dysbiosis influence neurotransmitter availability and neuroimmune signaling by decreasing short-chain fatty acids (SCFAs) and altering tryptophan metabolism. Another possible way in which phage bacteria may be involved in depressive phenomena is by regulating the production of neuromodulators such as serotonin and gamma-aminobutyric acid (GABA). Phage-induced increased bacterial turnover would enhance inflammatory signaling in the gut-brain axis (Cenit et al., 2017).

Autism Spectrum Disorder

ASD has been reported to exhibit marked variations in the gut microbiome, including reduced diversity and increased numbers of specific microbial species associated with the generation of neuroactive metabolites. It has also been proven that autistic people have evidence of enhanced intestinal permeability and translocation of microbial metabolites. Though the literature on the association between viruses and bacteria in ASD is limited, a few studies have identified altered viromes in children with ASD, suggesting that interactions between phages and bacteria can determine the stability of the microbiome during critical neurodevelopmental stages (Sharon et al., 2019).

7.4 Cancer and Immunotherapy Response.

Microbiome–Drug Interactions

The gut microbiota plays a role in the effectiveness and adverse effects of most cancer therapies, including immune checkpoint inhibitors. There are classes of bacteria that enhance immune responses against cancer by enhancing antigen presentation and T-cell activation. Phages may indirectly affect the success of general immunotherapy by altering the composition of bacterial populations, thereby influencing a person's

immune system. The genes of prophages alter how bacteria display their surface antigens and the metabolites they produce, thereby altering their recognition by an individual's immune system (Araji et al., 2022).

Phages and Tumor Microbiota

Bacteria related to tumors are detected in several types of cancers, including pancreatic (digestive) and colorectal cancer. The presence of bacteriophages (viruses that infect bacteria) in tumour microenvironments can influence the survival of bacterial populations and their capacity to form biofilms (colonies). Recent research suggests that phages may modify the architecture of bacteria in cancer, leading to changes in inflammation, immune cell infiltration, and response to therapy. The processes by which it occurs are yet to be known; hence, research on such phenomena is currently underway (Zhang et al., 2025).

Challenges and Future Perspectives in Microbiome–Phage Research

The study of the human microbiome has grown fast, yet bacteriophages are not yet completely incorporated into the theory of host-microbial interactions. Much research on microbiomes has focused on bacteria, and existing models often treat the virome as a secondary entity. Nonetheless, accumulating evidence indicates that phages have an active role in shaping the structure of microbial communities, their functional outputs, and ecosystem stability. The introduction of phages into models of microbiome necessitates the reorganization= of currently held ideas of dysbiosis, resilience, and host -microbe balance. The absence of complete characterisation of the viral diversity poses a significant technical limitation in microbiome-phage studies. Metagenomic surveys also indicate a steady rate of 40-90% of sequences that are virome-derived and cannot be classified to known taxa. This is indicative of a lack of universal viral marker genes, of great genetic diversity among phages, and of a lack of reference genome databases (Jankowski et al. 2025). As a result, most analyses are restricted to a small subset of known phages, limiting the ability to interpret changes in phage communities.

Methodological variability also limits inter-study comparisons. The inconsistency in the results across similar cohorts is due to variations in sample processing, viral enrichment, sequencing depth, assembly protocols, and bioinformatic pipelines. In contrast to bacterial microbiome research, there are still no standardized workflows for virome analysis. Better consistency between experimental and analytical methods will be required to enhance reproducibility (Yu et al., 2024).

The relationships between phages and bacteria are highly dependent on the environment. Models such as the kill-the-winner and piggyback-the-winner are helpful in describing these interactions, although their applicability depends on the density of the microbes, their spatial location, and the host's health. Phage activity at different intestinal locations, such as the lumen and mucus layer, varies, and inflammatory conditions may induce prophages, leading to a rapid shift in bacterial populations (Voigt et al.,2021). It is still not clear at what point phages promote stability and at what point they promote disruption. Neither is the behavior of phages toward the host immune system. Phages can also translocate across mucosal barriers, and mucosal phages are detected in systemic tissues, but how the immune system detects or tolerates them is not clearly understood. Although innate immune receptors (Toll-like receptors) might play a role, it is difficult to distinguish between direct effects on phages and indirect impact through bacteria. Therapeutically, there are further challenges associated with the use of phage-based strategies in complicated microbial ecosystems (Tang et al., 2025). Phage host specificity, the development of resistance, horizontal gene transfer, the activation of prophages, and unexpected impacts on microbial networks are to be taken into account. It remains to be seen what the long-term effects of changing phage populations in the gut might be. Future developments in the area will be based on integrating measures that connect changes in phage communities to both functional and host-level responses. Strain-resolved and longitudinal studies will be significant for understanding the dynamic interactions between phages and bacteria over time. Causality will require experimental systems to maintain the complexity of

microbes, such as humanized animal systems and more complex in vitro gut models. A transition to interpreting disease-related conditions as alterations in the regulation of microbial ecosystems, rather than merely changes in microbial composition, can improve understanding of host-microbiome-phage interactions and support the development of targeted interventions (Torres-Barceló, C. (2018).

Conclusion

The human microbiome is an ecosystem-level regulator of host physiology, including metabolic activity, immune signaling, and barrier integrity. Evidence synthesis conducted during the review of this paper has demonstrated that the presence or absence of certain microbes is not a determinant of health and disease, but rather the structure and regulation of specific microbial communities. The phageome plays a key role in this regulation and defines the structure of the bacterial population, gene flow, metabolic output, and, later, host-microbiome homeostasis. Microbiome-phage interference has been one of the most significant mechanisms underlying dysbiosis, contributing to the pathogenesis of chronic inflammation, metabolic dysregulation, and immune dysfunction. The recognition of bacteriophages as active and not passive biomarkers that characterize microbiome-associated disease, and the significance of employing ecosystem-based therapeutic modalities. Future perspectives will be based on integrating phage biology into the paradigm of microbiome studies, the emergence of strain-resolved and longitudinal studies, and the establishment of interventions that alter microbial networks rather than single taxa. This type of strategy will be required to ensure that microbiome-phage knowledge is relevant and applicable to specific, viable clinical practice.

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