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The Intestinal Virome and Immunity

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Abstract

The composition of the human microbiome is considered a major source of inter-individual variation in immunity, and by extension, susceptibility to diseases. Although intestinal bacteria have been the major focus of research, diverse communities of viruses that infect microbes and the animal host cohabitate the gastrointestinal tract, which collectively constitute the gut virome. Although viruses are typically investigated as pathogens, recent studies highlight a relationship between the host and animal viruses in the gut that is more akin to host-microbiome interactions and includes both beneficial and detrimental outcomes for the host. These viruses are likely sources of immune variation, both locally and extra-intestinally. In this review we describe the components of the gut virome, in particular mammalian viruses, and their ability to modulate host responses during homeostasis and disease.

Introduction

The human body harbors diverse populations of infectious entities, collectively known as the microbiome, that interact with each other and with the host to influence health and disease. While most commonly studied are the bacterial members of the microbiome, there are vast numbers of viruses present in the human body. Together, these viruses form the virome. Comprehensive annotation of the human virome is confounded by the staggering diversity of viruses detected at multiple anatomical sites that can have ssRNA, dsRNA, ssDNA or dsDNA genomes. Despite this challenge, recent advances in sequencing and analysis of metagenomic data have facilitated the discovery of new viruses and improved our ability to catalog viral communities in an unbiased manner (1, 2). These pioneering efforts reveal substantial intestinal virome diversity between individuals likely due to differences in bacterial composition and diet (3, 4). Studies comparing the virome between individuals have contributed to the growing evidence that differential exposure to viruses influences host physiology, either to the detriment or benefit of the host, much like the bacterial microbiome.

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Although the study of virology has generally focused on disease-causing animal viruses, a large fraction of the virome is comprised of bacteriophages and endogenous retroviral elements. Approximately 10^{15} bacteriophages exist in the human intestine (5). 10^{8}-10^{9} virus-like particles (VLPs) are found in a gram of human stool (6). The majority of these contain a DNA genome. Among the DNA viruses that can be matched to an annotated genome, 99% are bacteriophages and the remaining 1% are animal viruses such as anellovirus, parvovirus, adenovirus, and papillomavirus (6). Intrapersonal bacteriophage abundance is mostly stable over time but does show rapid sequence diversification (7). The predominant classifiable bacteriophage species in the gut are the dsDNA *Caudovirales* and ssDNA *Microviridae* (8). However, one uncharacterized dsDNA bacteriophage known as crAssphage is present in 73% of fecal metagenomes and predicted to infect *Bacteroides* species that are prevalent in the human gut (9, 10). In addition to directly influencing microbiome population dynamics by killing their bacterial hosts during lytic release of viral particles, bacteriophages that integrate into bacterial genomes contribute to the coding potential of the microbiome to indirectly influence the physiology of the animal host (8).

Endogenous retroviruses (ERVs) resemble present day exogenous retroviruses but are integrated in the host genome and transferred vertically between generations. They are estimated to comprise 8% of the human genome (11). The syncytin proteins that mediate placental development are derived from ERV *env* genes, and ERVs have dispersed interferon-inducible enhancer elements throughout mammalian genomes, suggesting that retroviral integration played a substantial role in mammalian evolution (12). Although most ERVs have accumulated many changes to their sequence over time that have rendered them defective, there are a limited number of ERVs with the potential to produce viral products that activate immune response or promote tumorigenesis (12–15). ERVs can also facilitate insertional mutagenesis and chromosomal rearrangements that affect cellular gene expression (16). The virome can also include plant viruses, likely introduced through food, and viruses that infect archaea and eukaryotic members of the microbiome such as fungi (mycobiome). One study showed that 97% of VLPs from the healthy human gut that harbor an RNA genome represent pathogenic plant viruses, with the remaining 3% belonging to animal viruses (17). How these viruses affect animal hosts is unknown.

The remainder of the virome consists of RNA and DNA animal viruses that are not integrated into the germ-line. At any given time, an individual human harbors multiple animal viruses, many of which establish chronic infections (18–20). The prevalence of animal viruses that cause transient infections, also considered part of the virome, can be more difficult to investigate, especially if the infection is asymptomatic. In contrast to serological methods that capture the infectious history of an individual (21), metagenomic studies may miss the contribution of a virus that is no longer present in a patient or diseased tissue. Additionally, chronic infections are often difficult to detect because certain viruses can exist in a quiescent state (latency), and the immune system may restrict replication to levels that are undetectable by conventional methods. In one of the few longitudinal virome studies performed to date, fecal samples from healthy human infants were shown to harbor RNA and DNA animal viruses belonging to 16 distinct families during the first 24 months of life (22). By adulthood, a typical individual will have been infected by at least 10 different viruses, with some individuals showing evidence of infection by 50-100 viral species (21).

The traditional paradigm of host-pathogen interactions, where infection by an individual agent directly produces immediate disease, fails to fully capture our relationship with many of these animal viruses. The necessity of the host machinery for their life cycle suggests that these viruses are unlikely to be silent passengers. Recent studies highlight how the gastrointestinal tract is an important site for virus-microbiome and virus-host interactions that likely contribute to inter-individual variation in immunity and disease susceptibility (Figure 1). Therefore, in this article we will focus on the impact of intestinal animal viruses as modifiers of the immune system. We will first review the pathways involved in recognition and responding to intestinal infection, and provide evidence of functional interactions between animal viruses and the bacterial microbiome. We will next discuss the beneficial and detrimental impact of intestinal infections by viruses beyond their role as pathogens. At the end, we use examples of how knowledge gained from the study of viral infections at non-intestinal sites can guide future research into the gut virome.

Immune responses to enteric viruses

Unlike bacteria, viruses need to infect host cells within the gastrointestinal tract to support their propagation. Target cells include the one-layer thick epithelial cells that serve the dual function of facilitating nutrient exchange and a physical barrier against invasion (23). Dendritic cells (DCs) and macrophages within the lamina propria (tissue underlying the epithelium) and gut-associated lymphoid tissue (GALT, such as Peyer's patches) also commonly encounter viruses (24). Nucleic acid derived from enteric viruses are sensed by these cells through many of the same pattern recognition receptors (PRRs) that are important at other sites. These include endosomal toll-like receptors (TLRs) that signal through MYD88 and TRIF, and the cytosolic sensors retinoic acid inducible gene–I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) that signal through MAVS, to stimulate the expression of type I (IFN-I) and type III (IFN-III) interferons (24). Both RIG-I and MDA5 are necessary for optimal antiviral responses to rotavirus, a dsRNA virus that infects the small intestinal epithelium to cause diarrheal disease in children (25). Sensing of ssRNA noroviruses, which also cause gastroenteritis in humans, can occur through MDA5, TLR7, and TLR3 in myeloid cells (26, 27). Although best known for responding to bacteria, recent studies suggest that cytosolic Nod-like receptors (NLRs) have an intestine-specific role in restricting viruses. Mice deficient in NLRP6, which can serve as a co-factor for RNA helicase DHX15 to signal through MAVS, display a blunted IFN-I/III response and are susceptible to oral infection by encephalomyocarditis virus (ECMV) and murine norovirus (MNV) (28). The multiple pathways involved in norovirus recognition may reflect inter-strain differences or their ability to infect broad cell types including myeloid cells, lymphocytes, and the specialized sensory epithelial cell known as tuft cells (29–32). Inhibiting the ability of MNV to engage these rare tuft cells prevents infection, highlighting the importance of an exquisitely specific cell tropism and remarkable adaptation of enteric viruses (30). Rotavirus RNA is sensed by NLRP9b and another RNA helicase DHX9 in the intestinal epithelium and is essential for inflammasome-mediated cell death (pyropotosis). Given that rotaviruses antagonize IFN signaling, this pathway may explain why other PRRs are inadequate for controlling this virus (33).

Despite the ability of certain viruses to evade IFN responses, numerous studies highlight the essential role of these cytokines during intestinal infection. IFN-I (IFNα and IFNβ) binds the interferon-α/β receptor (IFNAR1 and IFNAR2 complex) while IFN-III (IFNλ) binds the interferon lambda receptor (IFNLR1 and IL10R2 complex) to induce an antiviral gene expression program. Although the exact effector mechanisms in the gut remain obscure, they are presumably similar to other sites of infection and involve interferon stimulated genes (ISGs) that reduce viral replication (e.g., modification of viral RNA) and induce a refractory state in neighboring uninfected cells. IFNAR1 is broadly expressed on a variety of cell types, and is necessary for preventing systemic dissemination of MNV, rotavirus and reovirus (34). In contrast, the relatively restricted expression of IFNLR1 to epithelial cells suggests it has a more defined role in controlling mucosal viral replication (35). IFNλ, in combination with IL-22 production by group 3 innate lymphoid cells (ILC3s), effectively controls intestinal rotavirus infection (36). IFNλ signaling in epithelial cells is also required to regulate fecal shedding and viral replication in mice infected with MNV and reovirus (37). IFNs also promote adaptive immune responses (38), which are critical for control of enteric viruses (39–42). Suboptimal $CD8^+$ T cell responses and avoidance of $CD8^+$ T cell detection are associated with MNV persistence (43, 44). Furthermore, successful vaccination against rotavirus directly correlates with IgA production (45). Although we emphasize the role of cytokines downstream of PRRs in subsequent sections as a common means by which viruses affect host physiology, understanding how adaptive immunity functions or fails to control enteric viruses remains an important topic with direct relevance to vaccine efforts.

Boosting innate immunity may be an effective strategy for overcoming insufficient antiviral immunity in the gut. Treatment with bacterially-derived flagellin prevents and cures chronic rotavirus infection of mice by triggering IL-22 and IL-18 production through TLR5 and NLRC4, respectively (46). For noroviruses, effective antivirals and vaccines currently do not exist, and there is increased concern that persistent norovirus infection may be contributing to morbidity in immunocompromised individuals or facilitating transmission (47, 48) Remarkably, administration of recombinant IFNλ is sufficient to clear infection of a persistent strain of MNV independently of the adaptive immune response (29, 49). As we discuss throughout this article, the induction of IFNs is a hallmark of viral infection, and likely mediates many of the consequences of enteric viruses on host physiology.

Impact of bacteria on enteric virus infection

Depletion of intestinal bacteria often reduces the replication of enteric viruses, as the bacterial microbiome is known to facilitate viral infection and modify anti-viral immune responses (50, 51). Optimal poliovirus infectivity is dependent on the stabilization of virions upon binding to bacterial surface polysaccharides (52, 53). Binding to bacteria also promotes poliovirus attachment to target cells, which can enhance viral fitness by facilitating co-infection with multiple virions and genetic recombination events between viral strains (54). For similar reasons, intestinal titers and pathology are reduced following infection of antibiotics-treated *Ifnar1*$^{-/-}$ mice with reovirus (52). During vertical transmission of mouse mammary tumor virus (MMTV) through maternal milk, LPS bound to virions from the mother stimulates the production of the immunosuppressive cytokine IL-10 in the pups to allow the establishment of infection (55). Treatment of mice with antibiotics also decreases

intestinal MNV replication (32, 56, 57). Here, bacteria reduce the efficacy of IFNλ-mediated viral clearance and enhance infection of B cells (32, 56). During rotavirus infection, bacteria reduce systemic and intestinal anti-rotavirus IgA titers to support increased rotavirus replication (58). These studies indicate that animal viruses that infect the gastrointestinal tract have adapted to the presence of bacteria.

Beneficial impact of viruses in the gut

The importance of the microbiome to the intestinal environment is apparent in germ-free mice, which display numerous intestinal and immune abnormalities due to the lack of microbial communities (59). Germ-free mice and mice treated with antibiotics also show increased susceptibility to models of intestinal damage, peanut allergy, allergic asthma and bacterial infections (60–64). Although in some cases intestinal bacteria are sufficient to modulate these responses, in many models a role for the virome cannot be ruled out, especially given that antiviral signaling has a prominent role in diseases involving the gut. Non-hematopoietic expression of MAVS is required to protect mice against colitis following intestinal injury by dextran sodium sulfate (DSS) (65). Similarly, IFN-I signaling following stimulation of the MAVS and RIG-I pathways improves intestinal barrier function and protects mice from graft-vs-host disease (GVHD), a complication that occurs following allogeneic stem cell transplantation (66). In another example, administration of a TLR7 agonist enhances colonization resistance to vancomycin-resistant *Enterococcus* (VRE), a common hospital-acquired opportunistic pathogen, by stimulating dendritic cells that induce IL-22 production by ILC3s (27). Another example where intestinal viruses potentially promote colonization resistance was observed during fecal microbiome transplantation in patients harboring *Clostridium difficile*. Surprisingly, filtrated feces (to remove the bacterial component and retain viruses) have the same efficacy as un-filtrated feces in treating the patients (67). It is possible that the active component of the fecal microbiome transplantation (FMT) consists of bacteriophages because patients with *C. difficile* infection had altered bacteriophage abundance and richness compared to healthy controls, and successful transplantation was associated with transfer of *Caudovirales* species (68). These and other observations indirectly suggest that enteric viral infections fortify the intestinal barrier in certain situations via triggering beneficial immune responses or influences the bacterial microbiome.

Mechanistic experiments in mice, especially with MNV infections, provide formal evidence that viruses can function as a subset of the microbiome in a manner analogous to intestinal bacteria (Table I). Many MNV strains establish persistent infection in the intestine, frequently in the absence of obvious symptoms. Infection by a persistent strain of MNV compensates for the absence of bacteria in germ-free mice by restoring intestinal morphology and promoting lymphocyte differentiation (57). In addition, MNV protects antibiotics-treated mice from DSS-induced intestinal injury in a manner dependent on IFNAR1 (57). MNV can also protect antibiotics-treated mice from pathology during superinfection with the intestinal bacterial pathogen *Citrobacter rodentium* and reduces colonization by VRE (27, 57). The recent discovery that MNV infects tuft cells, which coordinates type 2 immune responses and mucus production, suggests that infection by this virus could directly influence the function of the intestinal epithelium and warrants further

investigation (30). It is possible that these effects extend beyond the gastrointestinal tract because MNV infection protects mice from lung injury following infection with *Pseudomonas aeruginosa* (69), and MNV restores serum immunoglobin in germ-free mice to levels observed in conventional mice (57). The observation that norovirus RNA is detected in up to 16% of healthy humans reinforces the need to understand how enteric viral infections impact host biology when they are not causing diarrheal disease (70).

Other animal viruses may also promote intestinal homeostasis. Treatment of mice with a cocktail of antivirals increases the severity of DSS-induced colitis, while treatment with inactivated rotavirus or TLR3/7 agonists reduces disease (71). In this case, the protective effect of TLR ligation was attributed to IFN-I expression by plasmacytoid DCs. This response to viruses may be conserved in humans because *TLR3* and *TLR7* gene variants are associated with increased severity of inflammatory bowel disease (IBD) in patients (71). Murine cytomegalovirus (CMV), a herpesvirus that chronically infects a variety of tissues and cell types, promotes turnover of the epithelium in multiple organs including the intestine. This effect was attributed to epithelial proliferation induced by the ISG *Apol9a/b* expressed by macrophages downstream of elevated IFN-I and was shown to enhance intestinal wound healing (72). When taken together, these studies show that IFN-I and other antiviral responses induce factors that promote intestinal epithelial health in addition to those that inhibit viral replication. Whether IFNs in the gut are beneficial to the host may be context-specific and not without controversy (24). A major future direction is to elucidate the specific mechanisms of action downstream of IFN signaling in the models described above.

Negative impact of viruses in the gut

Excess IFN-I production and other antiviral responses in the gut can potentiate disease (Table I). Until recently, IFN-I in combination with antiviral drugs was standard treatment for chronic hepatitis C virus (HCV) infection and was associated with significant toxicity, including gastrointestinal illness. There is also evidence from case studies to suggest that IFN-I therapy may potentiate the development of celiac disease, an autoimmune disorder that mainly occurs in individuals harboring HLA-DQ2 or DQ8 alleles where inappropriate responses to gluten leads to intestinal damage (73). This side effect of antiviral therapy is consistent with the observation that patients with celiac disease display increased levels of IFN-I production by intestinal DCs that promote Th1 responses in the gut (74). It is therefore unsurprising that virus infections have long been suspected to be involved in the development of celiac disease (75). A compelling recent study demonstrated that celiac disease may be caused by reoviruses, dsRNA viruses that commonly infect humans and typically associated with mild or undetectable disease (76). In an animal model, reovirus infection blocked the differentiation of peripheral regulatory T cells through IFN-I and enhanced dietary antigen-specific Th1 responses through the transcription factor interferon regulatory factor 1 (IRF1) (76). Patients with celiac disease were also more likely to have higher anti-reovirus antibody titers, which was associated with higher expression of IRF1 in the small intestinal mucosa (76). Therefore, enteric viruses that are otherwise tolerated may induce serious intestinal disease in susceptible individuals.

The paradigm of virus-plus-susceptibility gene interaction was initially demonstrated in experiments with MNV, and reinforces the concept that viruses function as members of the gut microbiome. A common variant of *ATG16L1*, a gene that mediates the cellular degradative pathway of autophagy, is associated with increased susceptibility to a form of IBD known as Crohn's disease. IBD is widely considered a disorder originating from a perturbed microbiome (77). *Atg16L1* mutant mice and Crohn's disease patients harboring the *ATG16L1* risk allele display morphological defects in Paneth cells (78), antimicrobial epithelial cells in the small intestine that are essential for preventing inflammation (79). In the *Atg16L1* mutant mice, the Paneth cell defects and other inflammatory pathologies were dependent on infection by MNV (78, 80). In this model, loss of *Atg16L1* in the intestinal epithelium sensitizes Paneth cells to necroptosis mediated by TNFα produced in response to viral infection (81). MNV also accelerates the onset of intestinal inflammation in mice deficient in the toxin transporter MDR1a that are colonized by *Helicobacter bilis* (82) and IL-10-deficient mice (83). Thus, immune responses to an otherwise beneficial or innocuous virus can contribute to intestinal disease when combined with genetic susceptibility.

Although host responses to MNV and Paneth cell properties are likely conserved between mice and humans, further evidence is required to support the role of IFN-I or the virome in Crohn's disease. A number of other viruses, including enterovirus, have been linked to Crohn's disease (84, 85). In a virome study, expansion of the *Caudovirales* bacteriophages in the gut was observed in Crohn's disease patients (86). Here, bacteriophage expansion was associated with decreased bacterial diversity suggesting that virus-microbiome interactions contribute to disease pathogenesis (86). A similar expansion of bacteriophage diversity is observed in patients with colorectal cancer and specific bacteriophage signatures can delineate patients in early or late stage and those with reduced survival (87). Also, a gut virome analysis of patients displaying GVHD with intestinal involvement revealed a marked increase in animal viruses with a DNA genome and bacteriophage richness (88). In particular, the presence of a dsRNA Picobirnaviridae species is predictive of a severe enteric disease (88). The combined approach of metagenomics through deep sequencing and targeted investigation of specific viral agents (like reovirus and celiac disease) may be necessary to explore the contribution of viruses to Crohn's disease, GVHD, and other complex inflammatory disorders that are likely influenced by multiple infectious and genetic factors.

Impact of intestinal viruses beyond the gastrointestinal tract

The impact of the intestinal virome may extend beyond the gastrointestinal tract to influence autoimmune diseases (Table I). One explanation for such extra-intestinal effects of viruses is the spread of infectious particles or viral RNA/DNA from the intestine to other body sites. Indeed, the transit of antigens between the gastrointestinal tract and pancreatic lymph nodes has been suggested as a mechanism for the effects of environmental agents on type 1 diabetes (T1D), an autoimmune disease where insulin-producing β cells are destroyed by pancreas-infiltrating autoreactive lymphocytes (89). Polymorphisms in MDA5 (*IFIH1*) and an IFN-I gene expression signature are associated with disease onset, supporting a role for viruses in disease progression (90, 91). Also, the appearance of autoantibodies in patients correlates with infection by coxsackievirus B1 (CVB1), a +ssRNA virus that belongs to a

diverse and prevalent group of picornaviruses that transmit fecal-orally (92). Infection with CVB3 and CVB6, which may provide cross-protection against CVB1, reduces the risk of T1D development in pre-diabetic children (92). Similar protection against virus-induced T1D is induced by CVB vaccination of mice (93). Although direct causation has not been established, CVB is believed to induce T1D by chronically infecting the pancreas and altering the local immune response (91). Rotavirus infection is also associated with progression to T1D (94). In the non-obese diabetic (NOD) mouse model of T1D, oral infection of adult mice with rotavirus leads to IFN-I-dependent bystander activation of lymphocytes in the pancreatic lymph nodes and acceleration of T1D onset, likely due to spread of infectious virus to the mesenteric and pancreatic lymph nodes (95–98). In contrast, neonatal infection of NOD mice with rotavirus or reovirus delays the onset of disease suggesting that timing of virus infections impacts the course of autoimmunity (99, 100).

A recent prospective study of infants at risk for T1D performed a longitudinal virome analysis and showed that increased bacteriophage diversity predicts a lack of progression to disease (101). Increased bacteriophage diversity correlated with changes in abundance of specific bacterial taxa, which may be related to the extensive literature using NOD mice demonstrating that the composition of the bacterial microbiome is an important factor in disease development (102). The same study also found an enrichment of sequences belonging to *Circoviridae* in the controls compared with individuals who develop T1D, raising the possibility that these group of poorly characterized small ssDNA animal viruses are protective (101). Although these studies implicate multiple viruses in disease pathogenesis, an exact mechanistic role for viruses in humans has yet to be established and requires additional research.

Metagenomic studies of HIV^+ individuals have been particularly informative in that they reveal the presence of a dynamic gut virome in a disease state. Low peripheral CD4 cells counts leads to the development of AIDS which is marked by increased susceptibility to secondary infection and other immunopathologies. The gut is a major site of HIV replication, HIV-specific immune responses and pathology (103). Enteric adenoviruses and anelloviruses are increased in HIV^+ patients with low peripheral $CD4^+$ T cell counts (104). Similar expansion of the virome is observed in primates infected with simian immunodeficiency virus (SIV), with intestinal adenovirus associated with increased enteritis and parvovirus viremia associated with increased progression to AIDS (105). It is possible that this increased presence of viruses contributes to AIDS in a manner similar to the proposed role of the bacterial microbiome, where depletion of T cells in the gut disrupt the barrier, leading to the systemic dissemination of bacterial products that fuel chronic and pathological immune activation (106). Given that the majority of humans by the time they reach adulthood become transiently or chronically infected by the animal viruses discussed in this section (*Anelloviridae*, *Adenoviridae*, and *Picornaviridae*), careful analyses of the gut virome in other immune-related disorders is warranted.

Lessons from extra-intestinal virus infection

When considering how the enteric virome might influence inter-individual variation, it is worth examining the known mechanisms by which viruses at other sites of the body alter the

immune system. Detailed immunological studies in mice have supported a role for the IFN response, but also highlight other pathways (Table II). Viruses that are traditionally considered to display localized infection and disease can provoke systemic responses, such as influenza A virus that induces hepatitis and intestinal damage without local infection (107, 108). Liver damage induced by influenza A virus is caused by the accumulation of pathogen-specific $CD8^+$ T cells and intestinal damage is the result of an altered bacterial microbiome and increased IL-17a (107, 108). Therefore, an important possibility to examine is whether enteric viruses select for T cells that exert pathological outcomes once they migrate to other sites.

Latent viral infections may be a particularly potent modulator of host responses. Gammaherpesvirus 68 (γHV-68) or CMV infection in mice enhances macrophage and NK cell activation, and improves the outcome of secondary infection with *Listeria monocytogenes*, *Yersinia pestis* and influenza A (109–111). In an animal model of primary immune-deficiency, latent γHV-68 infection rescues survival following *L. monocytogenes* infection by inducing an inflammatory reaction that compensates for inadequate cytokine levels, suggesting that deleterious mutations can be masked by an individual's virome (112). γHV-68 also protects against allergic asthma by altering the composition of macrophage subsets in the lung (113). In this case, the effect of viral infection was not dependent on latent infection and occurred during a developmental window. These findings in animal models are supported by elegant human cohort studies taking advantage of monozygotic twins with discrepancies in their history of exposure to infectious agents. CMV infection was identified as a particularly significant environmental variable that influences a broad range of immune parameters (114). Further, young adults previously exposed to CMV show a superior antibody and $CD8^+$ T cell response to influenza A vaccination (110). Thus, exposure to viruses can explain inter-individual heterogeneity when other factors fail to provide an adequate explanation.

The blood virome of healthy individuals include herpesviruses, anelloviruses, papillomaviruses, polyomaviruses, adenoviruses, parvoviruses and pegivirus (115, 116). Although it is unclear whether the presence of these viruses in the blood is consequential, the inverse relationship between pegivirus and HIV disease progression suggests that deeper investigation of the blood virome will be fruitful (117). In contrast, there is a wealth of examples demonstrating that respiratory viruses cause or exacerbate chronic lung diseases. In cystic fibrosis patients who display altered mucus production due to mutations in a chloride channel, disease is associated with the presence of a core group of bacteriophages that infect bacterial species persistent in lungs (118). Cystic fibrosis patients also show increased susceptibility to infection with rhinoviruses, which is linked to poor recovery of lung function following flares (119–121). Respiratory viruses are also linked to asthma (122). Patients have impaired IFN-I responses following rhinovirus infection, and rhinovirus C (RV-C) in particular is detectable in a significant proportion of children with moderate to severe asthma (122, 123). Consistent with this observation, the Y529 variant of cadherin-related family member 3 (CDHR3) that leads to increased binding of the virus to the lung epithelium confers susceptibility to RV-C-associated asthma (124, 125). As gene variants such as the loss of function allele of *fucosyltransferase 2* (*FUT2*) can determine whether

intestinal viruses bind cells (126, 127), an important area of research will be to examine how heritable factors affect the gut virome.

To summarize, virus-host interactions at extra-intestinal sites inform areas of future enteric virome research in the following ways. First, a number of these studies suggest that viruses that cause local infections such as in the lung have long range immunomodulatory effects. Therefore, examining the presence of viruses in affected tissues may not be sufficient, and a role for the gut virome should be considered. Second, the effect of a virus is not always apparent directly subsequent to virus exposure. This is clearly an important consideration for blood transfusions as viruses not routinely screened prior to blood donation could be transmitted to patients and have consequences for future disease pathogenesis. Perhaps similar concerns apply to FMTs that are routinely performed for *C. difficile* treatment and being considered for many other conditions. Finally, studies with CMV highlight the effect of viruses on the lymphocyte compartment and how adaptive immunity to subsequent antigens (i.e., not the original virus) may be altered. Molecular mimicry and bystander effects have been discussed extensively in other contexts (18), but are rarely considered downstream possibilities of intestinal virus infections in healthy individuals.

Conclusions

Significant progress has been made in the last decade towards understanding enteric viruses beyond their role as pathogens. While we continue to perform essential research into the pathogenic role of viruses and develop antivirals and vaccines, we can no longer ignore the possibility that they function as components of the microbiome. Like bacteria, the effects that viruses have are critically dependent on their tissue location, microenvironment and host. These factors will directly influence whether the virus acts beneficially, detrimentally or remains neutral for the host. With recent advances in metagenomics coupled with techniques that enrich in sensitivity (1, 2, 128), we can now preform large human studies with the aim of linking changes in specific viral populations with disease pathogenesis. These studies can then support the development of more defined animal and cell culture studies that address the mechanisms that individual viruses use to contribute to these phenotypes. This research will certainly lead to the discovery of novel ways in which viruses interact with the host that we can potentially harness for disease prevention and therapies. It may even be possible to engineer enteric viruses with desirable traits, much like current attempts at administering oncolytic viruses as adjuvants for cancer therapy (129–131).

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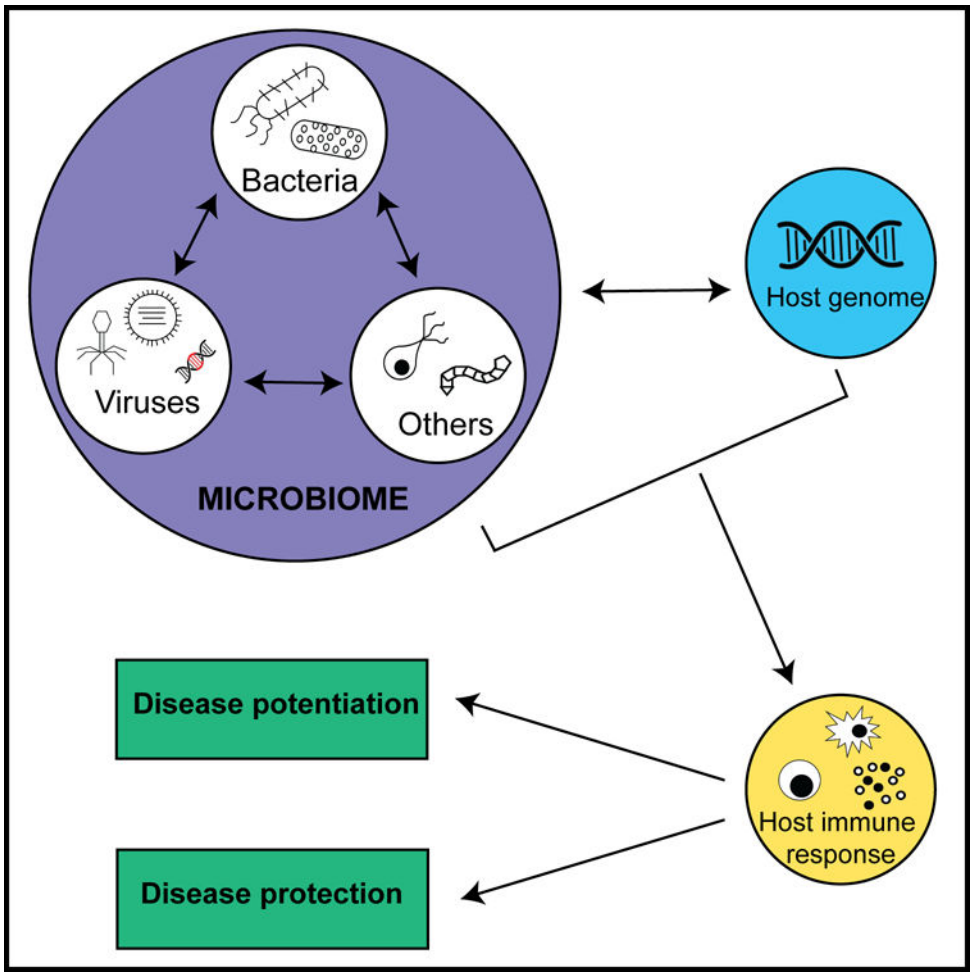

Figure 1. Virus-microbiome and virus-host genome interactions in immune variation

The host microbiome is a complex network of viruses, bacteria and other organisms (fungi, archaea, protozoans and helminths) that reside in the human body. The virome is comprised of animal viruses, bacteriophages and endogenous retroviruses. The gastrointestinal tract is inhabited by vast numbers of viruses and is an important site for virus-microbiome interactions and virus-host genome interactions. Intestinal bacteria interact with the virome by harboring bacteriophages and facilitating infection of barrier cells by animal viruses. Although typically investigated as pathogens, this review highlights how animal viruses in the gut serve as immune modulators that potentially explains inter-individual differences in disease susceptibility. The responses induced by various virus-microbiome and virus-host genome interactions likely alter the magnitude and function of the immune response to either the detriment or benefit of the host leading to either potentiation or protection from disease.

Table I

Examples in which intestinal viruses contribute to protection against or potentiation of diseases.

Virus	Model	Outcome	Mechanism	Reference
Murine norovirus (MNV)	Germ-free and broad-spectrum antibiotics-treated wild type mice	Restoration of intestinal architecture, immune cell populations, and resistance to chemically-induced colitis	Dependent on IFN-I	Kernbauer et al., 2014 (49)
	Ampicillin-treated wild type mice	Colonization resistance to *vancomycin-resistant enterococcus*	Increased IL-22^{+} ILC3	Abt et al., 2016 (19)
	Atg16L1 mutant mice	Crohn's like pathology in the small intestine	Paneth cell necroptosis due to virally-induced TNFα	Cadwell et al., 2010 (72) Matsuzawa-Ishimoto et al., 2017 (73)
	IL-10$^{-/-}$ mice	Intestinal inflammation	Dependent on bacteria	Basic et al., 2014 (75)
	H. bilis-infected MDR1a$^{-/-}$ mice	Intestinal inflammation	Unknown	Lencioni et al., 2008 (74)
	Wild type mice	Protection from lung damage following *P.* aeruginosa infection	Unknown	Thepaut et al., 2015 (61)
Reovirus	DQ8 transgenic mice and humans	Celiac disease manifestations	Suppression of peripheral Tregs and promotion of IRF1 and T_H1 immunity to dietary antigen	Bouziat et al., 2017 (68)
Caudovirales bacteriophage	Humans	Crohn's disease	Virus-microbiome interaction	Norman et al., 2015 (78)
		Successful treatment of *C. difficile* by FMT	Transfer of species from healthy donors	Zuo et al., 2017 (59)
Picobirnaviridae	Humans	Sever enteric GVHD	Unknown	Legoff et al., 2017 (79)
Coxsackievirus B	NOD mice	Accelerated autoimmune diabetes onset	Virus spread to the pancreas and local IFN-I response	Reviewed in Jean-Baptiste et al., 2017 (82)
Rotavirus	NOD mice	Accelerated autoimmune diabetes onset	IFN-I dependent bystander activation of lymphocytes in the pancreatic lymph nodes	Pane et al., 2014 (87) Pane et al., 2016 (88)
Circovirus	Humans	Protection from T1D	Unknown	Zhao et al., 2017 (92)
Adenovirus and anellovirus	Human	HIV disease progression	Unknown	Monaco et al., 2016 (95)

Animal models and observations in patients provide evidence for a role of intestinal viruses in modulating susceptibility to a range of disease conditions including intestinal inflammation (inflammatory bowel diseases, celiac disease and opportunistic colonization by antibiotic-resistance bacteria) and extra-intestinal disorders (T1D, lung infections, and HIV). Mechanisms frequently involve cytokines produced in response to viral infection that act on surrounding tissue or induce the mobilization of lymphoid cells. The outcome can be beneficial or detrimental to the host depending on whether a heightened state of immunity is desirable (e.g., protection against an infection versus fueling a chronic inflammatory disease). Abbreviations: IFN-1, type I interferon; ILC3, type 3 innate lymphoid cell; IRF1, interferon regulatory factor 1; FMT, fecal microbiome transplantation; NOD, non-obese diabetic; T1D, type 1 diabetes.

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Table II

Mechanisms by which extra-intestinal viruses contribute to protection against or potentiation of diseases.

Virus	Route of Infection	Model	Outcome	Mechanism	Reference
Cytomegalovirus (CMV)	Intraperitoneal	Wild type mice	Resistant to infection with the bacterial pathogens *Listeria monocytogenes* and *Yersinia pestis*	Latent infection, IFNγ expression and activation of systemic macrophages	Barton et al., 2007 (100)
			Intestinal proliferation	IFN-I mediated *Apol9a/b* expression	Sun et al., 2015 (64)
			Resistance to Influenza A infection	Mediated by IFNγ expression	Furman et al., 2015 (101)
Gammaherpesvirus 68 (γHV-68)	Intranasal	HOIL-1$^{-/-}$ mice	Rescues lethality to *Listeria monocytogenes*	Mediated by increased proinflammatory cytokines	MacDuff et al., 2015 (103)
	Intraperitoneal	Wild type mice	Resistant to infection with the bacterial pathogens *Listeria monocytogenes* and *Yersinia pestis*	Latent infection, IFNγ expression and activation of systemic macrophages	Barton et al., 2007 (100)
	Intranasal	Wild type mice	Protection from allergic asthma	Alteration of alveolar macrophage subsets	Machiels et al., 2017 (104)
Influenza A virus	Respiratory	Wild type mice	Collateral liver damage	Accumulation of virus-specific CD8^{+} T cells in the liver	Polakos et al., 2006 (98)
			Intestinal damage	Microbiota-dependent expression of IL-17a in the intestine	Wang et al., 2014 (99)
Rhinovirus C	Respiratory	Humans	Exacerbated asthma	Use of a specific receptor, CDHR3	Bizzintino et al., 2011 (114) Bochkov et al., 2015 (115)
	Respiratory	Humans	Cystic Fibrosis	Unknown	Goffard et al., 2014 (110)
Pegivirus	Blood	Humans	HIV disease protection	Unknown	Williams et al., 2004 (108)

Examples discussed in this article by which extra-intestinal viruses have unexpected immunomodulatory effects on the host are listed. As with intestinal viruses, these viruses can protect against infectious and non-infectious challenges, while simultaneously increasing susceptibility to autoimmune or inflammatory diseases. These examples highlight the ability of viruses to affect tissue outside their replicative niche, sometimes long after the initial infection, and suggest that enteric viral infections may have similar consequences for the host. Abbreviations: CDHR3, cadherin-related family member 3