Immunity
Review

The Virome in Host Health and Disease

Ken Cadwell[1,*]
[1]Kimmel Center for Biology and Medicine at the Skirball Institute, Department of Microbiology, New York University School of Medicine, New York, NY 10016, USA
*Correspondence: ken.cadwell@med.nyu.edu
http://dx.doi.org/10.1016/j.immuni.2015.05.003

The mammalian virome includes diverse commensal and pathogenic viruses that evoke a broad range of immune responses from the host. Sustained viral immunomodulation is implicated in a variety of inflammatory diseases, but also confers unexpected benefits to the host. These outcomes of viral infections are often dependent on host genotype. Moreover, it is becoming clear that the virome is part of a dynamic network of microorganisms that inhabit the body. Therefore, viruses can be viewed as a component of the microbiome, and interactions with commensal bacteria and other microbial agents influence their behavior. This piece is a review of our current understanding of how the virome, together with other components of the microbiome, affects the function of the host immune system to regulate health and disease.

Introduction

The collection of organisms inhabiting the human body, the microbiome, is an integral component of our physiology. In particular, the bacterial members of the microbiome are proposed to mediate phenotypic differences between individuals, much like gene variants in the host genome (Cho and Blaser, 2012). These symbiotic bacteria are in a position to have an influential impact on our biology because they are numerous, diverse, differ between individuals, and interact with the host and each other over a long period of time (Hooper and Gordon, 2001). These qualities also describe the collection of viruses that inhabit our body, and thus the virome is in a similar position as the bacterial microbiome to impact human health and disease.

By any criterion, the size and diversity of the virome is staggering. The mammalian virome includes viruses that infect cells of the animal host, endogenous viral elements, and viruses that infect members of the microbiome, most notably phages that replicate in bacteria (Virgin, 2014). All adult humans are chronically infected with multiple RNA and DNA animal viruses, ranging from traditional pathogens to those that usually are innocuous but are harmful in a small fraction of the population (Virgin et al., 2009). Viruses that fall into the categories of commensal and opportunistic pathogen include many that are detected in the majority of the adult human population, such as members of the herpesvirus, polyomavirus, adenovirus, circovirus, and anellovirus families (Bernardin et al., 2010; Garnett et al., 2002; Virgin et al., 2009; Wylie et al., 2014). Tragically, there are also millions of individuals chronically infected with viruses associated with high rates of morbidity and mortality such as HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) (Matthews et al., 2014). By establishing long-term infections, these diverse pathogenic and non-pathogenic animal viruses can be viewed as "contributing" to the host phenotype, and the presence of a subset might occasionally be beneficial.

The gastrointestinal tract in particular is a hotbed for transkingdom interactions due to the apposition of the mucosal immune system with viruses and microorganisms representing different kingdoms of life. The number of viral particles in human feces is in the same range as bacteria—upward of 10^9 per gram (Kim et al., 2011a). Most of these viral particles correspond to phages with extreme inter-individual variation, even when comparing first-degree relatives (Minot et al., 2011; Reyes et al., 2010). It is also clear that humans and other mammals harbor novel animal viruses in the intestine that remain to be characterized (Finkbeiner et al., 2008; Firth et al., 2014; Handley et al., 2012; Phan et al., 2011). Metagenomics studies of the intestine and other anatomical sites will continue to detect new sequences corresponding to viruses, including those that currently elude annotation.

In this review, recent findings indicating that the impact of the mammalian virome matches the extraordinary diversity of viruses that inhabit the body will be discussed. The immunomodulatory effect of viruses will be emphasized, especially those that have long-lasting consequences. There is also an emerging paradigm that viruses functionally interact with one another or other members of the microbiome to shape host immunity. Our current understanding of how these complex transkingdom interactions affect the host will be evaluated.

Immunomodulation by the Virome

Viral DNA and RNA trigger the production of interferons and other cytokines upon recognition by innate immune sensors. This initial response contributes to additional antiviral gene expression, antibody-mediated neutralization, and killing of virally infected cells by natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) (Takeuchi and Akira, 2009). To prevent an unrestricted antiviral immune response from causing excessive damage to the host, these classic antiviral effectors are coupled with production of immunosuppressive cytokines such as interleukin-10 (IL-10), regulatory T (Treg) cell activity, and upregulation of inhibitory receptors on effector T cells (Rouse and Sehrawat, 2010).

The objective of generating these soluble factors and mobilizing cells is to combat the virus with as little cost to the host as possible. However, induction of these effector and suppressor mechanisms also modifies the state of immunity, referred to herein as immunomodulation. Viral immunomodulation has consequences for the host beyond antiviral defense and can alter susceptibility to complex diseases and secondary infections. Immunomodulation in its simplest form is divided

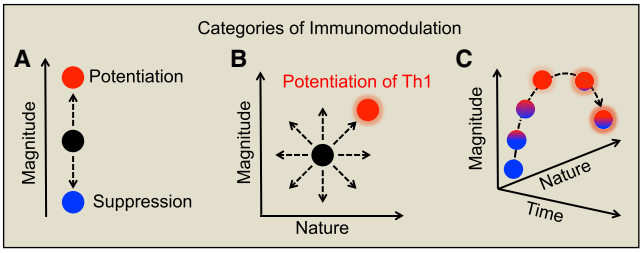

Figure 1. Categories of Viral Immunomodulation

The presence of a virus can shift the qualitative and quantitative state of immunity in multiple dimensions, thereby altering susceptibility to inflammatory diseases or subsequent infections.

(A) During immunopotentiation, a virus increases the magnitude of a subsequent response or decreases the threshold necessary to evoke a certain immune response. In contrast, immunosuppression occurs when the immune system is compromised and the magnitude of subsequent responses is diminished.

(B) In addition to magnitude, the nature of subsequent immune responses can be altered by previous viral infections. In the example shown, the presence of a virus shifts the state of immunity toward a more potent Th1 cell response. Another common outcome is sustained increase in type I interferon levels.

(C) Viral immunomodulation can change over time, occasionally returning to basal levels, but often not all the way back to the original point. Other dimensions of immunity that are subject to viral immunomodulation include anatomical site and T cell receptor and B cell receptor repertoires.

into immunopotentiation and immunosuppression, representing states of increased and decreased immunity, respectively (Figure 1A). In addition to shifting the magnitude of responses, viral immunomodulation can change the nature of immune reactions generated by the host, such as T helper (Th) cell polarization (Figure 1B). Although viral infections traditionally skew immunity toward Th1 cell, respiratory syncytial virus (RSV) can induce Th2 cell polarization in the lung (Culley et al., 2006). Also, preferential targeting of Th17 cells by HIV indicates that immunosuppression can have qualitative aspects as well (Prendergast et al., 2010). Immunomodulation can be local or systemic, change over time, alter the immunogenicity of antigens, and differ between anatomical compartments (Figure 1C). Potentiation of one branch of the immune system might come at the cost of another, and viral immunosuppression is often, if not always, accompanied by a heightened state of inflammation. Therefore, viral immunomodulation is complex and multidimensional.

Chronic infections are likely to delay or prolong immunomodulation. Many viruses establish latency, a state in which the viral genome persists within a cell without producing infectious viral particles. During latency, the virus is less visible due to decreased metabolic activity and amount of antigens available for detection by receptors of the innate and adaptive immune system. Viruses that display continuous replication employ other strategies to persist. HBV evokes an unusually low innate immune response by inhibiting multiple steps of the type I interferon (IFN-I) induction and signaling pathway, which probably allows this virus to reside in the liver over the lifetime of the infected individual (Busca and Kumar, 2014). Lymphocytic choriomenengitis virus (LCMV) and murine norovirus (MNV) strains that establish persistent infections in mice evoke suboptimal T cell responses compared with acute strains that are successfully eradicated (Tomov et al., 2013; Zajac et al., 1998). Cells harboring latent or actively replicating viruses are not necessarily restricted to a particular anatomical location. Viruses often infect cells of hematopoietic origin that circulate through the blood and lymph. Consequently, viral immunomodulation also occurs when a virus changes the function or number of lymphoid and myeloid cells by directly infecting these cell types.

Viruses that cause transient disease, such as measles virus, sometimes persist for a prolonged period in a subset of individuals (Griffin et al., 2012). It is also common to be infected by related viruses multiple times over the course of a lifetime, as observed with respiratory viral infections. For these reasons, it might be useful to consider viruses that are better known for causing acute disease as part of the virome, although the long-term immunomodulatory consequences of chronic viral infections are more obvious.

Deleterious Consequences of Viral Immunomodulation

The immune response to a virus sometimes resolves the infection with modest discomfort, as in the case of the common cold. In other instances, immune effectors cause substantial collateral damage in the form of tissue destruction, scarring, and organ failure. For chronic infections, the failure to completely remove the virus might lead to disease downstream of sustained immunopotentiation, as exemplified by liver fibrosis and cirrhosis caused by CTLs recognizing a continuous source of HCV and HBV antigens (Guidotti and Chisari, 2006). Infection can also promote immunosuppression that facilitates secondary infection. Depletion of $CD4^+$ T cells by HIV is a striking example of the catastrophic effects of viral immunosuppression (Maartens et al., 2014). Cancer is another deleterious consequence of viral immunomodulation. In addition to disrupting the integrity of the host genome or contributing oncogenes, as seen in human papillomavirus (HPV) infections that lead to cervical cancer (Frazer et al., 2011), viral infections promote tumorigenesis by altering the environment. Hepatocellular carcinoma is a downstream complication of HCV and HBV infection (Guidotti and Chisari, 2006). Also, Kaposi's sarcoma herpesvirus (KSHV) encodes several homologs of host proteins involved in immunity, such as viral IL-6 (vIL-6) and Fas-associated death domain-like IL-1-converting enzyme inhibitory protein (vFLIP), which stimulate angiogenesis and NF-κB signaling to create conditions that are favorable to the sarcoma and lymphomas associated with this virus (Ganem, 2010).

Given the diversity of viruses and the reactions they evoke from the host, it is likely that viral immunomodulation is a contributing factor for many of the complex inflammatory diseases that have an unknown etiology. For instance, lymphocytes reactive to Epstein-Barr virus (EBV) are enriched in affected tissue and serum from patients presenting several autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome, and multiple sclerosis (Draborg et al., 2013; Münz et al., 2009). The mechanism of these associations could involve cross-reactivity toward self-antigens by lymphocytes that were selected based on recognition of a viral antigen (molecular mimicry) or an adjuvant effect of the virus whereby the infection alters the environment (bystander activation) (Münz et al., 2009). This link between EBV and autoimmunity is controversial because of the ubiquitous presence of this herpesvirus in the healthy population and the difficulty in providing definitive evidence. Nevertheless, animal models support a role for molecular mimicry and bystander activation

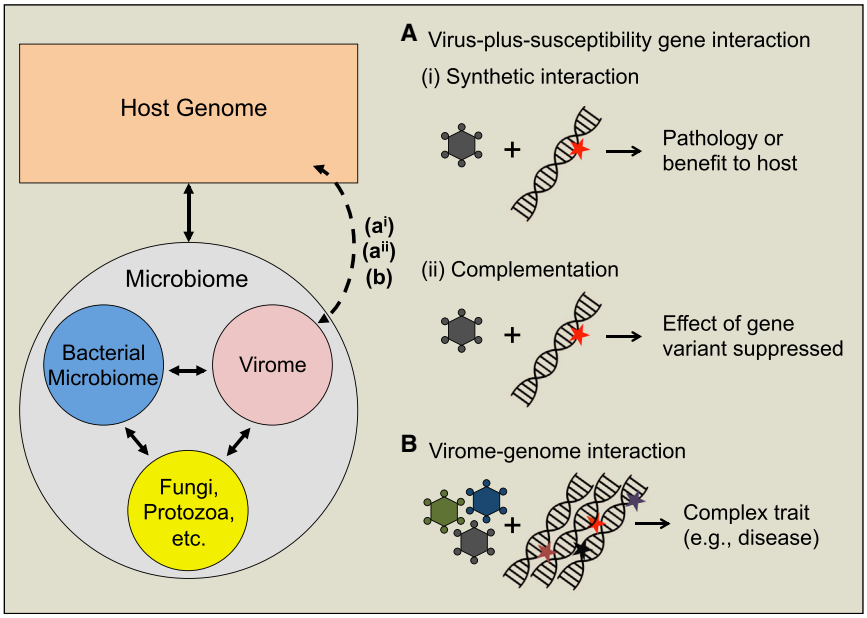

Figure 2. Types of Virome Interactions

The virome exists within the microbiome network and interacts with the bacterial microbiome and other organisms that inhabit the host such as fungi (mycobiome), archaea, protozoans, and helminths. The effect of the virome on the host genome represents a subset of the host genome-microbiome interaction. A simple relationship between the virome and host genome is the virus-plus-susceptibility-gene interaction, where a phenotypic outcome, such as a disease pathology or symptom, is evoked by the combination of a viral infection and host gene variant (a-i). In addition to this synthetic interaction, another type of virus-plus-susceptibility-gene interaction is phenotypic complementation, in which the viral infection masks the effect of a host gene variant (a-ii). Although examples are lacking, a virus could induce benefits in a manner dependent on a host gene variant, or negate the beneficial effect of a gene variant. In situations where the outcome is a complex disease or trait, the virome-genome interaction involves multiple viruses and host genetic variants (b). Some genetic variants exist in non-coding region and might influence gene expression in a manner dependent on viral infection. These interactions are influenced by other members of the microbiome, which regulate the activities of both the host and the virus.

as mechanisms by which autoimmunity arises downstream of immunomodulation by EBV or other viruses (Münz et al., 2009).

Genetic risk factors are insufficient to explain the origin of many inflammatory diseases, suggesting an essential role for environmental factors. Crohn's disease and ulcerative colitis, the two major types of inflammatory bowel disease (IBD), are proposed to be the result of an abnormal immune response to intestinal commensal bacteria (Huttenhower et al., 2014). Many of the IBD risk alleles occur in regions containing genes that have known functions in host-microbe interactions, such as the common T300A polymorphism in the autophagy gene *ATG16L1* associated with Crohn's disease (Huttenhower et al., 2014). Mice with decreased expression of *Atg16l1* develop intestinal abnormalities that are observed in Crohn's disease patients (Cadwell et al., 2008), but only in the presence of a persistent strain of MNV (Cadwell et al., 2010). In this model, *Atg16l1* mutation is associated with virus-induced inflammatory gene expression and cytokine activity rather than an increase in viral burden, implicating immunopotentiation. MNV also exacerbates intestinal inflammation in IL-10-deficient mice, a commonly used animal model of IBD (Basic et al., 2014). These observations demonstrate a virus-plus-susceptibility-gene interaction and introduce a potential role for an enteric virus in what is widely considered a disease dependent on intestinal bacteria (Huttenhower et al., 2014). If the virome is viewed as part of the microbiome instead of a separate entity, then this role for a virus is consistent with the extensive literature implicating the gut microbiome in IBD and is not mutually exclusive with a role for commensal bacteria (Figure 2).

A virus-plus-susceptibility-gene interaction can be highly specific. The above *Atg16l1* mutant mice do not develop intestinal abnormalities upon infection with a non-persistent strain of MNV (Cadwell et al., 2010), and the same mice are paradoxically protected from infection by the model enteric bacterial pathogen *Citrobacter rodentium* (Marchiando et al., 2013). Additionally, mice deficient in *Nod2*, another major Crohn's disease susceptibility gene, develop intestinal abnormalities due to immunomodulation by an ubiquitous intestinal bacterium *Bacteroides vulgatus* rather than MNV (Ramanan et al., 2014). Although it is unclear which specific members of the microbiome contribute to IBD in humans, it is possible that the exact offending infectious agent is dependent on the genotype of the patient, and in some cases, it might be a viral member of the microbiome rather than a bacterium that has the strongest role.

The virus-plus-susceptibility-gene interaction paradigm is the simplified version of the virome-genome interaction (Foxman and Iwasaki, 2011), where multiple viruses and alleles in the host genome dictate disease course in a combinatorial manner (Figure 2). In both humans and rodent models, a constellation of genetic and environmental factors including MHC haplotype promote the development of type 1 diabetes (T1D) (Concannon et al., 2009; Ghosh et al., 1993). A considerable number of epidemiological studies suggest that enteroviruses are one of the environmental susceptibility factors (Tauriainen et al., 2011). In support of a causal role, the enterovirus coxsackievirus B isolated from the pancreatic tissue of a diabetic child has been demonstrated to cause pancreatic islet β-cell death and diabetes in mice (Notkins et al., 1979). A virus does not necessarily have to infect the pancreas to trigger diabetes. Infection by rotavirus, a major cause of gastroenteritis in children, is associated with a concurrent increase in autoantibodies in children genetically at risk for T1D (Honeyman et al., 2000). In non-obese diabetic (NOD) mice with pre-existing autoimmunity, rhesus monkey rotavirus (RRV) accelerates diabetes by infecting lymph nodes and not the pancreas (Graham et al., 2008; Pane et al., 2013). This long-range immunopotentiation is probably mediated by IFN-I, which when produced by lymph node plasmacytoid dendritic cells that take up RRV, induces the activation of uninfected bystander dendritic cells, B cells, and autoreactive T cells (Pane et al., 2014). Consistent with this mechanism,

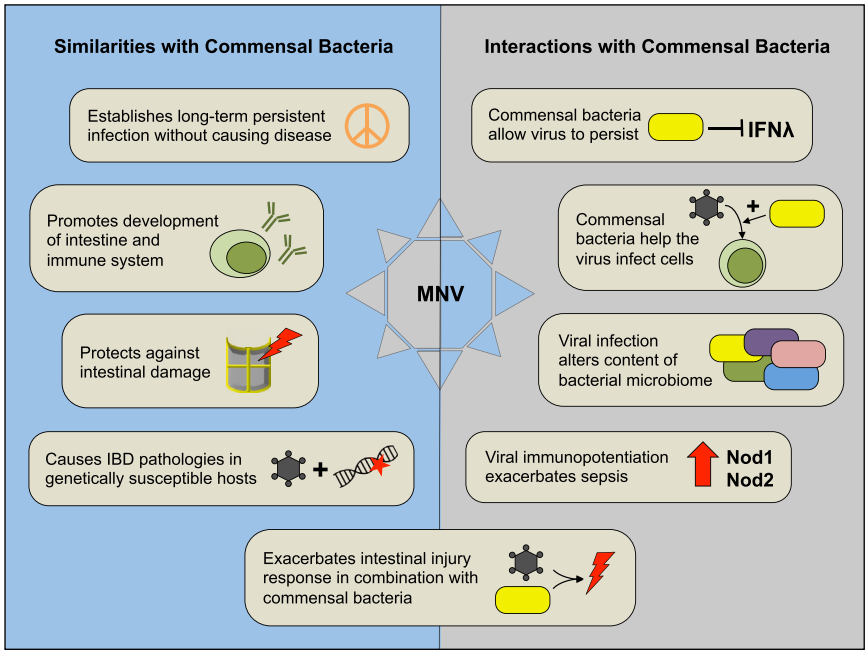

Figure 3. Relationship between Murine Norovirus and Commensal Bacteria

The enteric positive-strand RNA virus murine norovirus (MNV) displays similarities with commensal bacteria including the ability to establish long-term co-existence with the host without causing disease, to promote development of the intestine and associated immune system, to protect against chemical and infectious damage to the intestine, and to cause pathologies resembling inflammatory bowel disease (IBD) in genetically susceptible hosts (virus-plus-susceptibility-gene interaction). MNV also interacts with commensal bacteria, much like bacteria interact with one another. Examples of these interactions include the role of bacteria in promoting MNV persistence through blocking interferon-λ (IFN-λ) activity, the dependence of MNV on bacteria for binding and infecting cells, the ability of MNV to alter the relative abundance of bacterial populations, and immunopotentiation by MNV resulting in increased susceptibility to bacteria that enter circulation. Additionally, MNV exacerbates the intestinal injury response in the genetically susceptible host in a manner dependent on bacteria. This observation provides an example in which MNV interacts with the host together with commensal bacteria.

mutations that inhibit IFN-I production by the viral RNA sensor *IFIH1* (MDA5) protect against T1D development in humans (Nejentsev et al., 2009; Shigemoto et al., 2009).

Viruses that commonly infect infants and children are implicated in chronic lung disease. Severe lung infection by a rhinovirus in the first couple years of life has a strong correlation with development of asthma, and similar to T1D, susceptibility genes include those involved in viral recognition such as toll-like receptor 7 (TLR7) and TLR9 (Bartlett et al., 2009; Foxman and Iwasaki, 2011). Rhinovirus and Sendaivirus infections sensitize mice to airway inflammation resembling aspects of human asthma and chronic obstructive pulmonary disease (COPD) (Bartlett et al., 2008; Kim et al., 2008). All together, there is substantial evidence implicating the virome in a variety of chronic inflammatory diseases.

Many genetic variants associated with disease susceptibility occur in non-coding regions (Maurano et al., 2012). Systems biology approaches examining monocytes and dendritic cells indicate that common genetic variants affect the expression of hundreds of immune-related genes in a manner dependent on exposure to LPS, IFN-γ, influenza virus, or IFN-β (Fairfax et al., 2014; Lee et al., 2014). These findings suggest that genetic variants might be responsible for inter-individual differences in the transcriptional response to infectious stimuli including the virome.

Beneficial Effects of Viral Immunomodulation

Plant and insect viruses are known to confer key benefits to their hosts including protection from harsh weather conditions and pathogens (Roossinck, 2011). Experiments in mouse models indicate that viral immunomodulation is another way in which animal viruses benefit the host. Although viruses can accelerate pre-existing autoimmune diabetes, infecting young NOD mice with LCMV prevents disease through immunosuppression (Oldstone, 1988). Similarly, the γ-herpesvirus 68 (γHV68), a model for EBV and KSHV, protects against SLE-like disease (Larson et al., 2012). In contrast to this immunosuppressive activity, γHV68 confers protection against secondary infection by *Listeria monocytogenes* and *Yersinia pestis* by sustaining IFN-γ production and macrophage activation (Barton et al., 2007). Through a related mechanism, γHV68 infection reverses immunodeficiency in mice lacking the linear ubiquitin chain assembly complex (LUBAC) protein HOIL-1 (MacDuff et al., 2015), which is mutated in patients that display a spectrum of abnormalities including susceptibility to bacterial infections (Boisson et al., 2012). Thus, virus-plus-susceptibility-gene interaction can lead to a beneficial phenotypic complementation (Figure 2), and differences in the virome could partly explain how patients with Mendelian disorders can display different symptoms.

The concept that the virome is a subset of the microbiome is strengthened by the observation that MNV can replace many of the benefits provided by commensal bacteria in the intestine (Kernbauer et al., 2014). Germ-free mice and antibiotics-treated mice display developmental abnormalities in the intestine and associated mucosal immune system due to the absence of intestinal bacteria that provide important stimulatory signals (Hooper and Gordon, 2001). MNV infection of these mice that lack bacteria reverses these abnormalities and protects against intestinal injury caused by chemical insult or bacterial infection (Kernbauer et al., 2014). Therefore, this model intestinal virus displays many similarities with commensal bacteria such as those belonging to the *Bacteroides* genus—MNV can be a lifelong companion of the host, is typically innocuous but causes disease in genetic models of IBD, stimulates lymphoid differentiation, and is beneficial under certain conditions (Figure 3). As discussed below, another way in which MNV resembles commensal bacteria is that it interacts with other members of the gut microbiome.

Although virally induced IFN-I has been suggested to be detrimental in autoimmunity, the beneficial effects of MNV are dependent on the IFN-α receptor (Ifnar) (Kernbauer et al., 2014). In another example, the β-herpesvirus murine cytomegalovirus

(MCMV) raises the level of systemic IFN-I, which induces macrophage production of Apolipoprotein L9 molecules that stimulate epithelial proliferation in multiple organs (Sun et al., 2015). Although many of the IFN-stimulated genes (ISGs) induced by IFN-I signaling have known antiviral activity, a considerable number of them are poorly characterized. Examining the function of these genes and the intersection between IFN-I and other cytokines will be an important step toward elucidating mechanisms of viral immunomodulation.

Human noroviruses are unlikely to provide any benefits during the typical course of infection in which they are eliminated rapidly by the immune system after causing acute gastroenteritis. However, prolonged shedding of noroviruses has been detected in both immunocompromised and immunocompetent individuals, which has been suggested to contribute to the spread of the virus (Karst et al., 2014). Based on observations with MNV, it would also be important to consider immunomodulatory consequences of an extended asymptomatic infection. The effect of other enteric viruses detected in asymptomatic individuals has received even less attention. These questions have practical implications because viruses can be transferred during fecal transplantation procedures, which is used to treat *Clostridium difficile* colitis and being considered for other disorders (Pamer, 2014). Potential deleterious or beneficial consequences of transferring the virome require further investigation.

Immunomodulation by Endogenous Viral Elements and Phages

Although not the focus of this review, it is important to acknowledge the contribution of other members of the virome. Endogenous retroviruses (ERVs), the most common endogenous viral element, have had a major impact on mammalian evolution (Feschotte and Gilbert, 2012) and continue to affect our biology including immunity. For instance, when T-cell-independent antigens bind the B cell receptor (BCR), ERV RNA expression is induced, which triggers antiviral signaling that is necessary for IgM production (Zeng et al., 2014).

Bacterial, archaeal, fungal, and protozoan members of the microbiome are subject to infection by viruses, which constitute a substantive part of the mammalian virome (Zhang et al., 2006). Out of these, phages in the intestine have received the most attention in the context of the microbiome and immunity. Phages affect the mammalian host by killing susceptible pathogenic or commensal bacteria and mediate the exchange of virulence factors between bacteria through horizontal gene transfer (Duerkop and Hooper, 2013). Phages are enriched in the mucus overlaying the intestinal epithelium and are therefore in a position to provide an additional layer of defense to protect the barrier (Barr et al., 2013). Also, the mammalian immune system is capable of directly responding to large quantities of phages, but the physiological setting in which this occurs remains unknown (Duerkop and Hooper, 2013).

Much like bacterial dysbiosis, a term that refers to an imbalance in the composition of the microbiome, "viral dysbiosis" could be a marker of mucosal inflammation. IBD patients show an increase in richness (increase in taxa) of intestinal phages, especially members belonging to the Caudovirales order of double-stranded DNA phages (Norman et al., 2015). The lung virome (including both phages and animal viruses) is altered in individuals with cystic fibrosis (Willner et al., 2009). A deeper understanding of how phages interact directly or indirectly with the mammalian host will help determine whether altered phage content contributes to inflammatory disease.

Relationship between Animal Viruses and Commensal Bacteria

Enteric viruses evolved in the presence of bacteria and require their presence for efficient replication and transmission. Bacterial LPS and peptidoglycan stabilize the poliovirus virion and facilitate attachment to host cells (Kuss et al., 2011; Robinson et al., 2014). IL-10 is produced when TLR4 is activated by mouse mammary tumor virus (MMTV) bound to LPS, which mediates the immunosuppression necessary for viral transmission (Kane et al., 2011). Mice deficient in commensal bacteria also display reductions in reovirus pathogenicity and MNV replication (Figure 3; Baldridge et al., 2015; Jones et al., 2014; Kernbauer et al., 2014; Kuss et al., 2011). Consistent with these observations, the widely circulating GII.4 human norovirus strain infects cultured B cells, but only in the presence of commensal bacteria. Certain bacteria, such as *Enterobacter cloacae*, have surface glycoproteins homologous to histo-blood group antigens (HBGAs) that bind the virion to mediate attachment to host cells (Jones et al., 2014). Also, the bacterial microbiome promotes persistent infection of MNV through modulation of the antiviral activity of another IFN cytokine family member, IFN-λ (IFN-III) (Figure 3; Baldridge et al., 2015). Remarkably, IFN-λ is sufficient for sterilizing immunity to MNV (Nice et al., 2015).

Commensal bacteria can enhance host immunity to viruses. Altering the composition of gut bacteria with antibiotics decreases the $CD4^+$ T cell, $CD8^+$ T cell, and antibody responses to influenza lung infection by interfering with innate immune signals that act on migrating dendritic cells (Ichinohe et al., 2011). In another example, flagellin from commensal bacteria in the intestine act as an adjuvant that stimulates TLR5 and induces plasma cells to generate antibodies in response to inactivated influenza and polio vaccines (Oh et al., 2014). Activation of TLR5 with flagellin also prevents rotavirus infection and eliminates the virus from persistently infected mice by inducing an innate immune response through IL-22 and IL-18 (Zhang et al., 2014). A key future direction is to determine whether these mechanisms represent therapeutic targets for treating chronic viral infections in humans.

Viral immunomodulation can disrupt the balanced co-existence between the host and the bacterial microbiome. Mucosal T cell depletion by HIV and SIV infection leads to translocation of commensal bacteria through the intestinal epithelium, which fuels chronic inflammation and disease progression (Brenchley et al., 2006). MNV potentiates the inflammatory properties of otherwise innocuous bacteria in several situations (Figure 3). In the *Atg16l1* mutant mouse model, MNV causes IBD pathologies after intestinal injury in a manner dependent on commensal bacteria (Cadwell et al., 2010). Also, IFN-I induction by MNV leads to a lethal response to *E. coli* in a model of sepsis by increasing pro-inflammatory signaling through the bacterial sensors Nod1 and Nod2 (Kim et al., 2011b). Additionally, infection by an acute strain of MNV or human norovirus alters the composition of the bacterial microbiome (Hickman et al., 2014; Nelson et al., 2012). Given the proposed role of commensal

bacteria in a range of inflammatory and metabolic diseases, it will be important to determine whether transient or chronic infection by animal viruses cause long-lasting changes to the bacterial microbiome.

Viruses Interact with Helminths and Protozoans

Mammals have also co-evolved to tolerate the presence of helminth infections, which remains widespread among people living in developing countries. Infection of mice by *Schistosoma mansoni* and *Heligmosomoides polygyrus* induces the Th2 cytokine IL-4 that signals through the transcription factor Stat6, which specifically binds the γHV68 genome to reactivate the virus from latency (Reese et al., 2014). The ability to reactivate in the presence of IL-4 is conserved in KSHV, providing key evidence that viruses have adapted to the presence of helminths. Co-infection with MNV and the intestinal nematode *Trichenella spiralis* diminishes the numbers and effector functions of virus-specific $CD4^+$ and $CD8^+$ T cells (Osborne et al., 2014). This inhibitory effect of the helminth is independent of commensal bacteria. Instead, T cell suppression is mediated by the chitinase-like molecule YM1 produced by alternatively activated macrophages (AAMs) that are part of the Th2 cell response to *T. spiralis* (Osborne et al., 2014).

Although individuals living in industrialized nations today are less likely to be infected by helminths, therapeutic modalities involving helminths or their products are being considered for inflammatory diseases (Wolff et al., 2012). The effect of helminths on viruses needs to be considered when applying these intervention strategies. Additionally, the malarial parasite *Plasmodium falciparum* causes multiple molecular changes in germinal center B cells latently infected by EBV, which could explain why Burkitt's lymphoma is common in young children in tropical Africa (Torgbor et al., 2014). Understanding how protozoan and helminthic parasites affect the virome will continue to be relevant.

Intra-virome Interactions

Just as bacteria communicate with each other within the microbiome ecosystem, inter-virus interactions within the virome have been documented. EBV infection expands the pool of memory $CD8^+$ T cells that cross-react with antigens from other viruses such as influenza (Clute et al., 2005). Through a mechanism that resembles molecular mimicry in autoimmune disease, this cross-reactivity is associated with the pathological proliferation of activated $CD8^+$ T cells during infectious mononucleosis. The presence of such cross-reactive lymphocytes as well as other forms of viral immunomodulation have an immense influence on heterologous immunity to subsequent viral infections that can be either desired or unfavorable during vaccination (Selin et al., 2006). Viral infection can also alter the innate immune response to a second virus. Persistent LCMV infection reduces IFN-I production by plasmacytoid DCs and impairs the NK cell response to MCMV (Zuniga et al., 2008). EBV infection induces transcription of a superantigen encoded by the *env* gene of ERV-K18, leading to polyclonal T cell proliferation, providing an interesting example in which an ERV mediates immunomodulation by an exogenous virus (Stauffer et al., 2001).

The restructuring of the immune system by HIV and SIV has profound effects on the activity of other viruses. KSHV causes Kaposi's sarcoma in only a small percentage of immunocompetent individuals, but the incidence of this viral cancer is high in patients with AIDS and reversed by antiretroviral therapy (Ganem, 2010). AIDS caused by SIV infection leads to a substantial expansion of the enteric virome with the appearance of dozens of previously unknown animal viruses, indicating that primates harbor many intestinal viruses that are normally kept in check by the immune system (Handley et al., 2012). Similarly, an altered plasma virome, including an increase in anelloviruses and ERVs, is observed during human AIDS (Li et al., 2013). Together with commensal bacteria in the gut, these commensal viruses could have a pathological role in the chronic inflammation associated with disease progression. In contrast, some viruses are associated with slower HIV disease progression. The presence of GB virus C, a Flavivirus that can persist in immunocompromised individuals, significantly improves the outcome of HIV infection (Tillmann et al., 2001; Xiang et al., 2001). Also, the *Fv1* gene derived from the gag-region of an ERV confers resistance to murine leukemia virus (MLV) by binding the viral capsid (Best et al., 1996).

In addition to protecting against bacterial disease (Barton et al., 2007), herpesvirus infection is associated with improved antiviral immunity. A recent study found that young adults who are seropositive for human cytomegalovirus (HCMV) have elevated concentrations of circulating IFN-γ and other signs of increased antiviral immunity and displayed a superior antibody response to influenza vaccination (Furman et al., 2015). In this same study, MCMV infection of mice was found to reduce influenza virus replication and enhance the CD8 T cell response to influenza antigens, thereby validating the data obtained in humans. Better resolution of the human virome along with complementary functional studies in animal models will probably reveal many other synergistic and antagonistic relationships between viruses.

Toward a Holistic View of the Virome

Virology will continue to serve as an essential discipline that examines life-threatening pathogens. Nevertheless, the incredible progress in characterizing virus-host interactions highlighted in this article indicates that the virome is more than a collection of pathogens and includes viruses that function much like symbiotic bacteria. One key lesson from these studies has been that one virus could have multiple adverse and beneficial immunodulatory effects on the host that are dependent on the anatomical location, host genotype, and the presence of other infectious agents and commensal microbes (Figure 3). It is often the context that determines whether a virus is deleterious, neutral, or beneficial to the host. Although viruses are technically not organisms because they require the cellular machinery to replicate, it is helpful to view them as members of the microbial network that contributes to the host phenotype.

Another theme revealed by the literature discussed in this review is that the virome adds to the gene content and coding potential of the host (Figure 2). In the case of ERVs, the viral genome is literally part of the host genome. Retroviruses integrate into the host DNA and are part of the genome in infected cells. Herpesvirus and papillomavirus episomes that are attached to the host chromosome might not be too different in this sense, and some viruses that replicate outside the nucleus can contribute RNA and protein over long periods of time. Thus,

virus-plus-susceptibility-gene interactions and virome-genome interactions are expected outcomes of this co-existence. In some cases, a virus will evoke the effect of a genetic variant in the host in a manner analogous to synthetic lethality (MNV + *Atg16l1* mutation), where two mutations are necessary to yield a result. In other instances, a virus will mask the effect of a genetic variant (γHV68 + HOIL mutation), similar to genetic complementation.

There is little known about many of the viruses that inhabit us (many of which are yet to be discovered) because the research emphasis has been on viruses that cause obvious disease. With all the remaining questions surrounding human physiology and why certain individuals develop a given disease, can we afford to ignore these viruses? Examination of cell populations, serum proteins, and response to cytokine stimulation in samples collected from twins indicates that variation in the human immune response is largely driven by non-heritable factors (Brodin et al., 2015). Many of the inflammatory diseases in question are associated with industrialization or geography, and thus a changing virome could be one of the factors involved. A particular virus does not have to be the culprit in every incidence of the disease to be an important variable. For certain complex diseases like IBD, there might be multiple routes toward developing pathology, and a virus might be one of many contributing factors.

If viruses sway disease susceptibility in such a manner, then the following represent important goals of future virology.

(1) Cataloging the mammalian virome. Exposing associations between viruses and host traits requires knowing the diversity and prevalence of viruses that are present in the host. The technological hurdles are not trivial, but identification of viruses by deep sequencing is becoming more feasible due to decreasing costs and improvements in the bioinformatics pipelines.

(2) Establishing advanced in vitro infection models. Innovations in cell culture that mimic in vivo conditions such as organoids and 3D cultures will allow investigation of viruses that are otherwise difficult to examine. Once established, leukocytes and commensal bacteria can be added to these cultures to recreate multicellular and polymicrobial interactions.

(3) Identifying novel properties of viruses in animal models. Animal models and model viruses such as LCMV and MNV will continue to reveal unappreciated effects of viral immunomodulation and transkingdom interactions that are apparent only in an intact organism.

(4) Including measurements of viruses in systems-level analyses. Quantification of multiple parameters in a well-defined human cohort can be used to identify complex interactions between genetic and environmental variables. When the host, virus, and other members of the microbiome are examined together, a more complete picture of mammalian biology will emerge.

It is important not to lose sight of the fact that the virome includes many serious pathogens. Generating effective antivirals and vaccines will remain a research priority for many years to come, and evidence that viral infection has beneficial effects should not be used to interfere with these efforts. Instead, we should strive to understand the pathways and factors that determine whether a virus has a deleterious or advantageous impact on the host. This advanced understanding will assist in the design of therapies based on immunomodulation that can be applied to both viral and non-viral diseases.

ACKNOWLEDGMENTS

K.C. is supported by NIH grant R01 DK093668 and American Heart Association grant 12GRNT12030041. The author would like to thank P'ng Loke, Elisabeth Kernbauer, Jessica Pane, Timothy Nice, Tiffany Reese, and Namiko Abe for helpful comments on the manuscript. Special thanks to This Week in Virology (TWiV) for reminding us that biology makes the most sense when you include viruses in the discussion.

REFERENCES

Baldridge, M.T., Nice, T.J., McCune, B.T., Yokoyama, C.C., Kambal, A., Wheadon, M., Diamond, M.S., Ivanova, Y., Artyomov, M., and Virgin, H.W. (2015). Commensal microbes and interferon-λ determine persistence of enteric murine norovirus infection. Science *347*, 266–269.

Barr, J.J., Auro, R., Furlan, M., Whiteson, K.L., Erb, M.L., Pogliano, J., Stotland, A., Wolkowicz, R., Cutting, A.S., Doran, K.S., et al. (2013). Bacteriophage adhering to mucus provide a non-host-derived immunity. Proc. Natl. Acad. Sci. USA *110*, 10771–10776.

Bartlett, N.W., Walton, R.P., Edwards, M.R., Aniscenko, J., Caramori, G., Zhu, J., Glanville, N., Choy, K.J., Jourdan, P., Burnet, J., et al. (2008). Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. Nat. Med. *14*, 199–204.

Bartlett, N.W., McLean, G.R., Chang, Y.S., and Johnston, S.L. (2009). Genetics and epidemiology: asthma and infection. Curr. Opin. Allergy Clin. Immunol. *9*, 395–400.

Barton, E.S., White, D.W., Cathelyn, J.S., Brett-McClellan, K.A., Engle, M., Diamond, M.S., Miller, V.L., and Virgin, H.W., 4th. (2007). Herpesvirus latency confers symbiotic protection from bacterial infection. Nature *447*, 326–329.

Basic, M., Keubler, L.M., Buettner, M., Achard, M., Breves, G., Schröder, B., Smoczek, A., Jörns, A., Wedekind, D., Zschemisch, N.H., et al. (2014). Norovirus triggered microbiota-driven mucosal inflammation in interleukin 10-deficient mice. Inflamm. Bowel Dis. *20*, 431–443.

Bernardin, F., Operskalski, E., Busch, M., and Delwart, E. (2010). Transfusion transmission of highly prevalent commensal human viruses. Transfusion *50*, 2474–2483.

Best, S., Le Tissier, P., Towers, G., and Stoye, J.P. (1996). Positional cloning of the mouse retrovirus restriction gene Fv1. Nature *382*, 826–829.

Boisson, B., Laplantine, E., Prando, C., Giliani, S., Israelsson, E., Xu, Z., Abhyankar, A., Israël, L., Trevejo-Nunez, G., Bogunovic, D., et al. (2012). Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. Nat. Immunol. *13*, 1178–1186.

Brenchley, J.M., Price, D.A., Schacker, T.W., Asher, T.E., Silvestri, G., Rao, S., Kazzaz, Z., Bornstein, E., Lambotte, O., Altmann, D., et al. (2006). Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat. Med. *12*, 1365–1371.

Brodin, P., Jojic, V., Gao, T., Bhattacharya, S., Angel, C.J., Furman, D., Shen-Orr, S., Dekker, C.L., Swan, G.E., Butte, A.J., et al. (2015). Variation in the human immune system is largely driven by non-heritable influences. Cell *160*, 37–47.

Busca, A., and Kumar, A. (2014). Innate immune responses in hepatitis B virus (HBV) infection. Virol. J. *11*, 22.

Cadwell, K., Liu, J.Y., Brown, S.L., Miyoshi, H., Loh, J., Lennerz, J.K., Kishi, C., Kc, W., Carrero, J.A., Hunt, S., et al. (2008). A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature *456*, 259–263.

Cadwell, K., Patel, K.K., Maloney, N.S., Liu, T.C., Ng, A.C., Storer, C.E., Head, R.D., Xavier, R., Stappenbeck, T.S., and Virgin, H.W. (2010). Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell *141*, 1135–1145.

Cho, I., and Blaser, M.J. (2012). The human microbiome: at the interface of health and disease. Nat. Rev. Genet. *13*, 260–270.

Clute, S.C., Watkin, L.B., Cornberg, M., Naumov, Y.N., Sullivan, J.L., Luzuriaga, K., Welsh, R.M., and Selin, L.K. (2005). Cross-reactive influenza virus-specific CD8+ T cells contribute to lymphoproliferation in Epstein-Barr virus-associated infectious mononucleosis. J. Clin. Invest. *115*, 3602–3612.

Concannon, P., Rich, S.S., and Nepom, G.T. (2009). Genetics of type 1A diabetes. N. Engl. J. Med. *360*, 1646–1654.

Culley, F.J., Pennycook, A.M., Tregoning, J.S., Hussell, T., and Openshaw, P.J. (2006). Differential chemokine expression following respiratory virus infection reflects Th1- or Th2-biased immunopathology. J. Virol. *80*, 4521–4527.

Draborg, A.H., Duus, K., and Houen, G. (2013). Epstein-Barr virus in systemic autoimmune diseases. Clin. Dev. Immunol. *2013*, 535738.

Duerkop, B.A., and Hooper, L.V. (2013). Resident viruses and their interactions with the immune system. Nat. Immunol. *14*, 654–659.

Fairfax, B.P., Humburg, P., Makino, S., Naranbhai, V., Wong, D., Lau, E., Jostins, L., Plant, K., Andrews, R., McGee, C., and Knight, J.C. (2014). Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. Science *343*, 1246949.

Feschotte, C., and Gilbert, C. (2012). Endogenous viruses: insights into viral evolution and impact on host biology. Nat. Rev. Genet. *13*, 283–296.

Finkbeiner, S.R., Allred, A.F., Tarr, P.I., Klein, E.J., Kirkwood, C.D., and Wang, D. (2008). Metagenomic analysis of human diarrhea: viral detection and discovery. PLoS Pathog. *4*, e1000011.

Firth, C., Bhat, M., Firth, M.A., Williams, S.H., Frye, M.J., Simmonds, P., Conte, J.M., Ng, J., Garcia, J., Bhuva, N.P., et al. (2014). Detection of zoonotic pathogens and characterization of novel viruses carried by commensal *Rattus norvegicus* in New York City. MBio *5*, e01933–e14.

Foxman, E.F., and Iwasaki, A. (2011). Genome-virome interactions: examining the role of common viral infections in complex disease. Nat. Rev. Microbiol. *9*, 254–264.

Frazer, I.H., Leggatt, G.R., and Mattarollo, S.R. (2011). Prevention and treatment of papillomavirus-related cancers through immunization. Annu. Rev. Immunol. *29*, 111–138.

Furman, D., Jojic, V., Sharma, S., Shen-Orr, S.S., L Angel, C.J., Onengut-Gumuscu, S., Kidd, B.A., Maecker, H.T., Concannon, P., Dekker, C.L., et al. (2015). Cytomegalovirus infection enhances the immune response to influenza. Sci. Transl. Med. *7*, 81ra43.

Ganem, D. (2010). KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. J. Clin. Invest. *120*, 939–949.

Garnett, C.T., Erdman, D., Xu, W., and Gooding, L.R. (2002). Prevalence and quantitation of species C adenovirus DNA in human mucosal lymphocytes. J. Virol. *76*, 10608–10616.

Ghosh, S., Palmer, S.M., Rodrigues, N.R., Cordell, H.J., Hearne, C.M., Cornall, R.J., Prins, J.B., McShane, P., Lathrop, G.M., Peterson, L.B., et al. (1993). Polygenic control of autoimmune diabetes in nonobese diabetic mice. Nat. Genet. *4*, 404–409.

Graham, K.L., Sanders, N., Tan, Y., Allison, J., Kay, T.W., and Coulson, B.S. (2008). Rotavirus infection accelerates type 1 diabetes in mice with established insulitis. J. Virol. *82*, 6139–6149.

Griffin, D.E., Lin, W.H., and Pan, C.H. (2012). Measles virus, immune control, and persistence. FEMS Microbiol. Rev. *36*, 649–662.

Guidotti, L.G., and Chisari, F.V. (2006). Immunobiology and pathogenesis of viral hepatitis. Annu. Rev. Pathol. *1*, 23–61.

Handley, S.A., Thackray, L.B., Zhao, G., Presti, R., Miller, A.D., Droit, L., Abbink, P., Maxfield, L.F., Kambal, A., Duan, E., et al. (2012). Pathogenic simian immunodeficiency virus infection is associated with expansion of the enteric virome. Cell *151*, 253–266.

Hickman, D., Jones, M.K., Zhu, S., Kirkpatrick, E., Ostrov, D.A., Wang, X., Ukhanova, M., Sun, Y., Mai, V., Salemi, M., and Karst, S.M. (2014). The effect of malnutrition on norovirus infection. MBio *5*, e01032–e13.

Honeyman, M.C., Coulson, B.S., Stone, N.L., Gellert, S.A., Goldwater, P.N., Steele, C.E., Couper, J.J., Tait, B.D., Colman, P.G., and Harrison, L.C. (2000). Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. Diabetes *49*, 1319–1324.

Hooper, L.V., and Gordon, J.I. (2001). Commensal host-bacterial relationships in the gut. Science *292*, 1115–1118.

Huttenhower, C., Kostic, A.D., and Xavier, R.J. (2014). Inflammatory bowel disease as a model for translating the microbiome. Immunity *40*, 843–854.

Ichinohe, T., Pang, I.K., Kumamoto, Y., Peaper, D.R., Ho, J.H., Murray, T.S., and Iwasaki, A. (2011). Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc. Natl. Acad. Sci. USA *108*, 5354–5359.

Jones, M.K., Watanabe, M., Zhu, S., Graves, C.L., Keyes, L.R., Grau, K.R., Gonzalez-Hernandez, M.B., Iovine, N.M., Wobus, C.E., Vinjé, J., et al. (2014). Enteric bacteria promote human and mouse norovirus infection of B cells. Science *346*, 755–759.

Kane, M., Case, L.K., Kopaskie, K., Kozlova, A., MacDearmid, C., Chervonsky, A.V., and Golovkina, T.V. (2011). Successful transmission of a retrovirus depends on the commensal microbiota. Science *334*, 245–249.

Karst, S.M., Wobus, C.E., Goodfellow, I.G., Green, K.Y., and Virgin, H.W. (2014). Advances in norovirus biology. Cell Host Microbe *15*, 668–680.

Kernbauer, E., Ding, Y., and Cadwell, K. (2014). An enteric virus can replace the beneficial function of commensal bacteria. Nature *516*, 94–98.

Kim, E.Y., Battaile, J.T., Patel, A.C., You, Y., Agapov, E., Grayson, M.H., Benoit, L.A., Byers, D.E., Alevy, Y., Tucker, J., et al. (2008). Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. Nat. Med. *14*, 633–640.

Kim, M.S., Park, E.J., Roh, S.W., and Bae, J.W. (2011a). Diversity and abundance of single-stranded DNA viruses in human feces. Appl. Environ. Microbiol. *77*, 8062–8070.

Kim, Y.G., Park, J.H., Reimer, T., Baker, D.P., Kawai, T., Kumar, H., Akira, S., Wobus, C., and Núñez, G. (2011b). Viral infection augments Nod1/2 signaling to potentiate lethality associated with secondary bacterial infections. Cell Host Microbe *9*, 496–507.

Kuss, S.K., Best, G.T., Etheredge, C.A., Pruijssers, A.J., Frierson, J.M., Hooper, L.V., Dermody, T.S., and Pfeiffer, J.K. (2011). Intestinal microbiota promote enteric virus replication and systemic pathogenesis. Science *334*, 249–252.

Larson, J.D., Thurman, J.M., Rubtsov, A.V., Claypool, D., Marrack, P., van Dyk, L.F., Torres, R.M., and Pelanda, R. (2012). Murine gammaherpesvirus 68 infection protects lupus-prone mice from the development of autoimmunity. Proc. Natl. Acad. Sci. USA *109*, E1092–E1100.

Lee, M.N., Ye, C., Villani, A.C., Raj, T., Li, W., Eisenhaure, T.M., Imboywa, S.H., Chipendo, P.I., Ran, F.A., Slowikowski, K., et al. (2014). Common genetic variants modulate pathogen-sensing responses in human dendritic cells. Science *343*, 1246980.

Li, L., Deng, X., Linsuwanon, P., Bangsberg, D., Bwana, M.B., Hunt, P., Martin, J.N., Deeks, S.G., and Delwart, E. (2013). AIDS alters the commensal plasma virome. J. Virol. *87*, 10912–10915.

Maartens, G., Celum, C., and Lewin, S.R. (2014). HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet *384*, 258–271.

MacDuff, D.A., Reese, T.A., Kimmey, J.M., Weiss, L.A., Song, C., Zhang, X., Kambal, A., Duan, E., Carrero, J.A., Boisson, B., et al. (2015). Phenotypic complementation of genetic immunodeficiency by chronic herpesvirus infection. eLife *4*.

Marchiando, A.M., Ramanan, D., Ding, Y., Gomez, L.E., Hubbard-Lucey, V.M., Maurer, K., Wang, C., Ziel, J.W., van Rooijen, N., Nuñez, G., et al. (2013). A deficiency in the autophagy gene Atg16L1 enhances resistance to enteric bacterial infection. Cell Host Microbe *14*, 216–224.

Matthews, P.C., Geretti, A.M., Goulder, P.J., and Klenerman, P. (2014). Epidemiology and impact of HIV coinfection with hepatitis B and hepatitis C viruses in Sub-Saharan Africa. J. Clin. Virol. *61*, 20–33.

Maurano, M.T., Humbert, R., Rynes, E., Thurman, R.E., Haugen, E., Wang, H., Reynolds, A.P., Sandstrom, R., Qu, H., Brody, J., et al. (2012). Systematic localization of common disease-associated variation in regulatory DNA. Science *337*, 1190–1195.

Minot, S., Sinha, R., Chen, J., Li, H., Keilbaugh, S.A., Wu, G.D., Lewis, J.D., and Bushman, F.D. (2011). The human gut virome: inter-individual variation and dynamic response to diet. Genome Res. *21*, 1616–1625.

Münz, C., Lünemann, J.D., Getts, M.T., and Miller, S.D. (2009). Antiviral immune responses: triggers of or triggered by autoimmunity? Nat. Rev. Immunol. *9*, 246–258.

Nejentsev, S., Walker, N., Riches, D., Egholm, M., and Todd, J.A. (2009). Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. Science *324*, 387–389.

Nelson, A.M., Walk, S.T., Taube, S., Taniuchi, M., Houpt, E.R., Wobus, C.E., and Young, V.B. (2012). Disruption of the human gut microbiota following Norovirus infection. PLoS ONE *7*, e48224.

Nice, T.J., Baldridge, M.T., McCune, B.T., Norman, J.M., Lazear, H.M., Artyomov, M., Diamond, M.S., and Virgin, H.W. (2015). Interferon-λ cures persistent murine norovirus infection in the absence of adaptive immunity. Science *347*, 269–273.

Norman, J.M., Handley, S.A., Baldridge, M.T., Droit, L., Liu, C.Y., Keller, B.C., Kambal, A., Monaco, C.L., Zhao, G., Fleshner, P., et al. (2015). Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell *160*, 447–460.

Notkins, A.L., Yoon, J., Onodera, T., and Jenson, A.B. (1979). Virus-induced diabetes mellitus: infection of mice with variants of encephalomyocarditis virus, coxsackievirus B4, and reovirus type 3. Adv. Exp. Med. Biol. *119*, 137–146.

Oh, J.Z., Ravindran, R., Chassaing, B., Carvalho, F.A., Maddur, M.S., Bower, M., Hakimpour, P., Gill, K.P., Nakaya, H.I., Yarovinsky, F., et al. (2014). TLR5-mediated sensing of gut microbiota is necessary for antibody responses to seasonal influenza vaccination. Immunity *41*, 478–492.

Oldstone, M.B. (1988). Prevention of type I diabetes in nonobese diabetic mice by virus infection. Science *239*, 500–502.

Osborne, L.C., Monticelli, L.A., Nice, T.J., Sutherland, T.E., Siracusa, M.C., Hepworth, M.R., Tomov, V.T., Kobuley, D., Tran, S.V., Bittinger, K., et al. (2014). Coinfection. Virus-helminth coinfection reveals a microbiota-independent mechanism of immunomodulation. Science *345*, 578–582.

Pamer, E.G. (2014). Fecal microbiota transplantation: effectiveness, complexities, and lingering concerns. Mucosal Immunol. *7*, 210–214.

Pane, J.A., Webster, N.L., Graham, K.L., Holloway, G., Zufferey, C., and Coulson, B.S. (2013). Rotavirus acceleration of murine type 1 diabetes is associated with a T helper 1-dependent specific serum antibody response and virus effects in regional lymph nodes. Diabetologia *56*, 573–582.

Pane, J.A., Webster, N.L., and Coulson, B.S. (2014). Rotavirus activates lymphocytes from non-obese diabetic mice by triggering toll-like receptor 7 signaling and interferon production in plasmacytoid dendritic cells. PLoS Pathog. *10*, e1003998.

Phan, T.G., Kapusinszky, B., Wang, C., Rose, R.K., Lipton, H.L., and Delwart, E.L. (2011). The fecal viral flora of wild rodents. PLoS Pathog. *7*, e1002218.

Prendergast, A., Prado, J.G., Kang, Y.H., Chen, F., Riddell, L.A., Luzzi, G., Goulder, P., and Klenerman, P. (2010). HIV-1 infection is characterized by profound depletion of CD161+ Th17 cells and gradual decline in regulatory T cells. AIDS *24*, 491–502.

Ramanan, D., Tang, M.S., Bowcutt, R., Loke, P., and Cadwell, K. (2014). Bacterial sensor Nod2 prevents inflammation of the small intestine by restricting the expansion of the commensal *Bacteroides vulgatus*. Immunity *41*, 311–324.

Reese, T.A., Wakeman, B.S., Choi, H.S., Hufford, M.M., Huang, S.C., Zhang, X., Buck, M.D., Jezewski, A., Kambal, A., Liu, C.Y., et al. (2014). Coinfection. Helminth infection reactivates latent γ-herpesvirus via cytokine competition at a viral promoter. Science *345*, 573–577.

Reyes, A., Haynes, M., Hanson, N., Angly, F.E., Heath, A.C., Rohwer, F., and Gordon, J.I. (2010). Viruses in the faecal microbiota of monozygotic twins and their mothers. Nature *466*, 334–338.

Robinson, C.M., Jesudhasan, P.R., and Pfeiffer, J.K. (2014). Bacterial lipopolysaccharide binding enhances virion stability and promotes environmental fitness of an enteric virus. Cell Host Microbe *15*, 36–46.

Roossinck, M.J. (2011). The good viruses: viral mutualistic symbioses. Nat. Rev. Microbiol. *9*, 99–108.

Rouse, B.T., and Sehrawat, S. (2010). Immunity and immunopathology to viruses: what decides the outcome? Nat. Rev. Immunol. *10*, 514–526.

Selin, L.K., Brehm, M.A., Naumov, Y.N., Cornberg, M., Kim, S.K., Clute, S.C., and Welsh, R.M. (2006). Memory of mice and men: CD8+ T-cell cross-reactivity and heterologous immunity. Immunol. Rev. *211*, 164–181.

Shigemoto, T., Kageyama, M., Hirai, R., Zheng, J., Yoneyama, M., and Fujita, T. (2009). Identification of loss of function mutations in human genes encoding RIG-I and MDA5: implications for resistance to type I diabetes. J. Biol. Chem. *284*, 13348–13354.

Stauffer, Y., Marguerat, S., Meylan, F., Ucla, C., Sutkowski, N., Huber, B., Pelet, T., and Conrad, B. (2001). Interferon-alpha-induced endogenous superantigen. a model linking environment and autoimmunity. Immunity *15*, 591–601.

Sun, L., Miyoshi, H., Origanti, S., Nice, T.J., Barger, A.C., Manieri, N.A., Fogel, L.A., French, A.R., Piwnica-Worms, D., Piwnica-Worms, H., et al. (2015). Type I interferons link viral infection to enhanced epithelial turnover and repair. Cell Host Microbe *17*, 85–97.

Takeuchi, O., and Akira, S. (2009). Innate immunity to virus infection. Immunol. Rev. *227*, 75–86.

Tauriainen, S., Oikarinen, S., Oikarinen, M., and Hyöty, H. (2011). Enteroviruses in the pathogenesis of type 1 diabetes. Semin. Immunopathol. *33*, 45–55.

Tillmann, H.L., Heiken, H., Knapik-Botor, A., Heringlake, S., Ockenga, J., Wilber, J.C., Goergen, B., Detmer, J., McMorrow, M., Stoll, M., et al. (2001). Infection with GB virus C and reduced mortality among HIV-infected patients. N. Engl. J. Med. *345*, 715–724.

Tomov, V.T., Osborne, L.C., Dolfi, D.V., Sonnenberg, G.F., Monticelli, L.A., Mansfield, K., Virgin, H.W., Artis, D., and Wherry, E.J. (2013). Persistent enteric murine norovirus infection is associated with functionally suboptimal virus-specific CD8 T cell responses. J. Virol. *87*, 7015–7031.

Torgbor, C., Awuah, P., Deitsch, K., Kalantari, P., Duca, K.A., and Thorley-Lawson, D.A. (2014). A multifactorial role for P. falciparum malaria in endemic Burkitt's lymphoma pathogenesis. PLoS Pathog. *10*, e1004170.

Virgin, H.W. (2014). The virome in mammalian physiology and disease. Cell *157*, 142–150.

Virgin, H.W., Wherry, E.J., and Ahmed, R. (2009). Redefining chronic viral infection. Cell *138*, 30–50.

Willner, D., Furlan, M., Haynes, M., Schmieder, R., Angly, F.E., Silva, J., Tammadoni, S., Nosrat, B., Conrad, D., and Rohwer, F. (2009). Metagenomic analysis of respiratory tract DNA viral communities in cystic fibrosis and non-cystic fibrosis individuals. PLoS ONE *4*, e7370.

Wolff, M.J., Broadhurst, M.J., and Loke, P. (2012). Helminthic therapy: improving mucosal barrier function. Trends Parasitol. *28*, 187–194.

Wylie, K.M., Mihindukulasuriya, K.A., Zhou, Y., Sodergren, E., Storch, G.A., and Weinstock, G.M. (2014). Metagenomic analysis of double-stranded DNA viruses in healthy adults. BMC Biol. *12*, 71.

Xiang, J., Wünschmann, S., Diekema, D.J., Klinzman, D., Patrick, K.D., George, S.L., and Stapleton, J.T. (2001). Effect of coinfection with GB virus C on survival among patients with HIV infection. N. Engl. J. Med. *345*, 707–714.

Zajac, A.J., Blattman, J.N., Murali-Krishna, K., Sourdive, D.J., Suresh, M., Altman, J.D., and Ahmed, R. (1998). Viral immune evasion due to persistence of activated T cells without effector function. J. Exp. Med. *188*, 2205–2213.

Zeng, M., Hu, Z., Shi, X., Li, X., Zhan, X., Li, X.D., Wang, J., Choi, J.H., Wang, K.W., Purrington, T., et al. (2014). MAVS, cGAS, and endogenous retroviruses in T-independent B cell responses. Science *346*, 1486–1492.

Zhang, T., Breitbart, M., Lee, W.H., Run, J.Q., Wei, C.L., Soh, S.W., Hibberd, M.L., Liu, E.T., Rohwer, F., and Ruan, Y. (2006). RNA viral community in human feces: prevalence of plant pathogenic viruses. PLoS Biol. *4*, e3.

Zhang, B., Chassaing, B., Shi, Z., Uchiyama, R., Zhang, Z., Denning, T.L., Crawford, S.E., Pruijssers, A.J., Iskarpatyoti, J.A., Estes, M.K., et al. (2014). Viral infection. Prevention and cure of rotavirus infection via TLR5/NLRC4-mediated production of IL-22 and IL-18. Science *346*, 861–865.

Zuniga, E.I., Liou, L.Y., Mack, L., Mendoza, M., and Oldstone, M.B. (2008). Persistent virus infection inhibits type I interferon production by plasmacytoid dendritic cells to facilitate opportunistic infections. Cell Host Microbe *4*, 374–386.