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Immunomodulation by Enteric Viruses

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Abstract

Enteric viruses display intricate adaptations to the host mucosal immune system to successfully reproduce in the gastrointestinal tract and cause maladies ranging from gastroenteritis to life-threatening disease upon extraintestinal dissemination. However, many viral infections are asymptomatic, and their presence in the gut is associated with an altered immune landscape that can be beneficial or adverse in certain contexts. Genetic variation in the host and environmental factors including the bacterial microbiota influence how the immune system responds to infections in a remarkably viral strain–specific manner. This immune response, in turn, determines whether a given virus establishes acute versus chronic infection, which may have long-lasting consequences such as susceptibility to inflammatory disease. In this review, we summarize our current understanding of the mechanisms involved in the interaction between enteric viruses and the immune system that underlie the impact of these ubiquitous infectious agents on our health.

1. INTRODUCTION

Enteric viruses, defined broadly as viruses that infect cells of the gastrointestinal tract in animals, have long been appreciated as etiological agents of acute gastroenteritis. Infections are generally self-resolving but can be life-threatening when the affected individual is immunocompromised or lacks adequate access to healthcare. Their impact on society is exemplified by the success of vaccination against rotavirus. In the four-year period following introduction of rotavirus vaccination in 2006, the vaccines are estimated to have prevented 176,000 hospitalizations and 1.1 million outpatient visits among children under 5 years of age in the United States, saving approximately $1 billion in healthcare costs (1, 2). Tragically, viral gastroenteritis still accounts for over 200,000 childhood deaths per year worldwide. Only a handful of effective pharmaceutical interventions exist, and most treatment regimens address hydration status. The impact of enteric viruses is even greater when considering their effect on our health when they leave the gut to cause extraintestinal disease. Most poliovirus infections are asymptomatic or lead to mild symptoms such as fever and headache. However, approximately 1 in 200 individuals develops paralytic poliomyelitis. Endemic poliovirus persists in regions where vaccine delivery is not feasible, and a recent case of paralytic disease in an unvaccinated individual in New York is a reminder that this enterovirus is still a danger.

The ubiquitous presence of enteric viruses in healthy individuals and those with chronic conditions suggests that our understanding of our relationship with these infectious agents is incomplete. Sensitive techniques such as shotgun sequencing consistently detect a multitude of sequences aligning to DNA and RNA viruses in stool specimens, rivaling the diversity and density of the bacterial microbiome. Phages that replicate in bacteria represent most of the gut virome, defined as the collection of intestinal viruses in a given host. Bacteriophages are detected as early as one month after birth, coinciding with the first bacterial colonizers of the gut, which is followed by animal viruses by four months (3, 4). Bacteriophages impact animal hosts by lysing bacteria (e.g., *Escherichia coli* strains associated with colorectal cancer), by altering properties of their bacterial host (e.g., phage integration into *Enterococcus gallinarum* induces mucus production), or through direct recognition by the mammalian immune system (5–7). However, as infectious agents that require animal cells to replicate, enteric animal viruses that infect cells of the gastrointestinal tract may have a larger role in shaping our immune landscape, which is the focus of this review.

In this article, we discuss mechanisms by which enteric viruses that infect animal cells interact with and affect the host immune system. We provide an overview of common enteric viruses that infect humans and their associated diseases, and we summarize mechanisms of virus-immune crosstalk. Additionally, we discuss how host genetics and the microbiota shape immune reactions and consequences of enteric virus infection. Finally, we provide our perspective on future directions in the field.

2. ANATOMY OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract is a hollow muscular tube that extends from the oral cavity to the anus. The inside of the tube is referred to as the lumen, and the cells that serve as the lining are the epithelial cells. The main purposes of the gastrointestinal tract are to break down food, absorb nutrients, and expel waste. The gastrointestinal tract consists of several organs, each with specific functions and unique epithelial cell types (8) (**Figure 1**).

The oral cavity is where mechanical and chemical breakdown of food occurs to initiate digestion. Salivary glands secrete saliva containing enzymes such as amylase to begin breaking down carbohydrates. The pharynx, the part of the throat behind the mouth and nasal cavity, leads into the esophagus, which propels food toward the stomach through peristalsis. The stomach

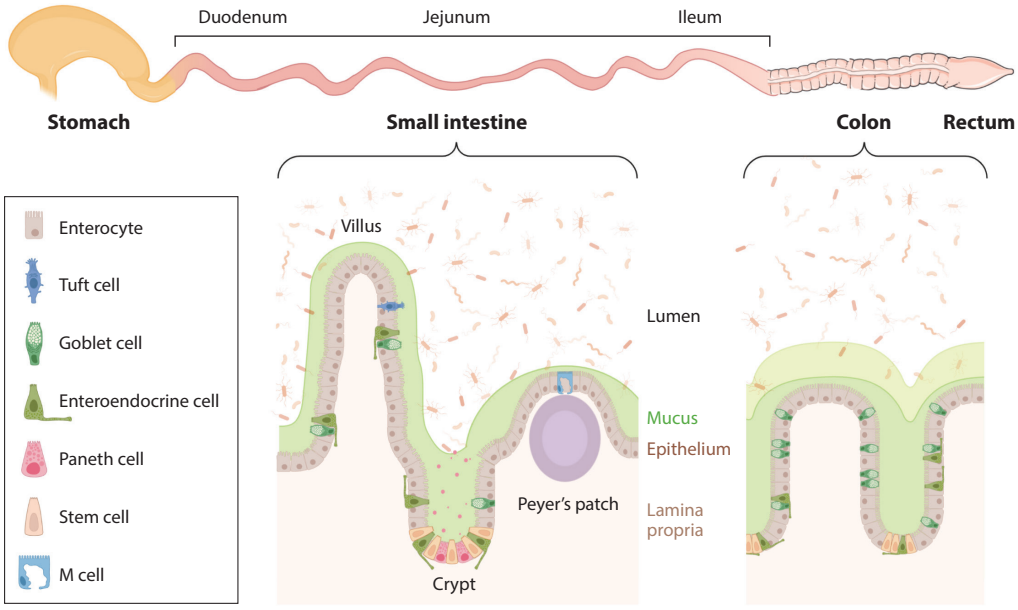

Figure 1

Overview of the lower gastrointestinal tract. Enteric viral infections typically affect the small intestine (duodenum, jejunum, and ileum) and colon where a single-layer epithelium separates the connective tissue (lamina propria) from the lumen. In the small intestine, the epithelium protrudes in long villi covered with a loose layer of mucus produced by goblet cells for maximal nutrient absorption. In between villi are crypts that contain the epithelial stem cells. The villi become progressively shorter toward the ileum and are absent in the colon. In the small intestine, Paneth cells producing antimicrobial peptides in the crypts and the presence of Peyer's patches contributes to protection from microorganisms. The colon lacks villi but has extended crypts covered by a thick bilayered mucus. Abbreviation: M cell, microfold cell. Figure adapted from Reference 193 (CC BY 4.0) using images created with BioRender.com.

is responsible for mixing and storing food while it is being broken down by gastric secretions. The stomach's inner lining forms gastric pits and glands containing parietal cells that produce hydrochloric acid and intrinsic factor, chief cells that secrete pepsinogen to break down proteins, goblet cells that produce mucus to protect the stomach lining, and enteroendocrine cells that secrete hormones and other signaling molecules to regulate digestion.

The viruses discussed in this article and the immune response are mainly associated with the small intestine and colon, collectively referred to as the lower gastrointestinal tract. The small intestine is the primary site of nutrient absorption and is divided into three segments: duodenum, jejunum, and ileum. Finger-like projections termed villi extend into the lumen to further increase the surface area for absorption, and in between the villi are pits known as crypts of Lieberkühn where the epithelial stem cells reside. The small intestine also contains structures called Peyer's patches, which are aggregates of lymphoid tissue involved in adaptive immunity. There are six lineages of intestinal epithelial cells (IECs) derived from a common stem cell progenitor in the small intestine: enterocytes, the most abundant IECs with apical microvilli to favor nutrient absorption; mucus-secreting goblet cells; Paneth cells with antimicrobial granules, located in the small intestinal crypts to protect adjacent stem cells; enteroendocrine cells mentioned above; chemosensory tuft cells; and microfold cells localized to Peyer's patches, where they participate in antigen sampling by mediating trafficking of substrates across their membranes in a process termed transcytosis (**Figure 1**).

The large intestine, also known as the colon, absorbs water and electrolytes from the remaining indigestible food and forms feces. It consists of the cecum, colon, rectum, and anal canal. The

large intestine does not have villi and has elongated crypts with numerous goblet cells instead. The rectum stores feces before expulsion through the anus. For both the small and large intestines, a single layer of IECs separates the lumen from the lamina propria (connective tissue) and the rest of the body. A large number of immune cells are found both in between epithelial cells and within the lamina propria, poised to respond to and neutralize ingested pathogens. This reactivity is balanced with mechanisms that prevent unwanted reactions against food antigens and the microbiota. When the balance between defense and tolerance is disrupted, the host may become susceptible to infections or experience collateral damage from immune reactions, as observed in food allergies or inflammatory bowel disease (IBD). Enteric viruses successfully navigate this complex immune landscape, including functionally interacting with the bacterial microbiota.

3. OVERVIEW OF ENTERIC VIRUSES

The main families of animal viruses detected in the human gut virome include *Reoviridae* (rotaviruses and reoviruses), *Caliciviridae* (noroviruses and sapoviruses), *Adenoviridae* (adenoviruses), *Astroviridae* (astroviruses), *Picornaviridae* (poliovirus, coxsackieviruses, echoviruses, and other enteroviruses), *Herpesviridae* (cytomegalovirus), *Anelloviridae* (anelloviruses), and *Circoviridae* (circoviruses) (3, 4, 9, 10). Noroviruses, sapoviruses, rotaviruses, astroviruses, and some adenovirus strains replicate locally in the gut and represent established causative agents of acute gastroenteritis. Other viruses, most notably *Picornaviridae*, replicate in the gut but cause diseases only after they disseminate to other anatomical sites. The converse can also occur when viruses reach the gut from another region of the body. Below, we provide an overview of prominent viruses belonging to these categories.

3.1. Viruses Associated with Acute Gastroenteritis

Infections by agents of viral gastroenteritis discussed below occur following ingestion of contaminated food or water. In addition to feces from an infected individual, new evidence suggests viral shedding from the salivary gland is an important route of transmission (11). Symptoms include vomiting, diarrhea, fever, and abdominal pain. Infections can be lethal in vulnerable individuals such as young children.

3.1.1. Rotavirus and reovirus. Rotaviruses are nonenveloped and have a double-stranded (ds) RNA genome with 11 segments encoding 6 structural viral proteins (VP1, 2, 3, 4, 6, 7), which form the multilayered virions, and 6 nonstructural proteins (NSP1–6) involved in viral replication and immune evasion (12). After uncoating of the outer layer of the virion upon entry, messenger RNA (mRNA) synthesis and protein translation occur in the cytosol followed by viral replication in perinuclear cytosolic inclusions (13). The characteristic watery diarrhea, due to defects in fluid secretion, is attributed to the release of ADP following the disruption of intracellular Ca^{2+} stores by NSP4 (14). Rotaviruses replicate in enterocytes at the tip of villi, and viral RNAs are detected in other IECs such as tuft cells (12, 15). The vaccines against human rotavirus are live-attenuated or generated through reassortment with the bovine rotavirus, and although safe and effective, they are less successful in low- and middle-income countries for reasons that remain unclear (16). Reoviruses (orthoreoviruses) belong to the same viral family as rotaviruses and share similar genomic features and replication strategy. They rarely cause severe symptoms in humans, but they can infect the central nervous system (CNS) in mouse neonates, which is lethal (17).

3.1.2. Norovirus and sapovirus. With the introduction of the rotavirus vaccine, noroviruses (type strain Norwalk virus) became the predominant cause of viral gastroenteritis in many parts of the world including the United States (18). Noroviruses are nonenveloped positive-sense,

single-stranded (+ssRNA) viruses. Their environmental stability facilitates transmission, especially wherever people live in close quarters such as cruise ships, nursing homes, and military barracks. Immunocompromised individuals such as transplant recipients display chronic infection and disease (19). In this setting, the virus is detected in enteroendocrine cells (20). Persistent asymptomatic infections, which may be more prevalent than previously appreciated, can lead to shedding of virus in stool for weeks, potentially contributing to new outbreaks (18, 21). The first open reading frame (ORF) of the 7.4- to 7.7-kb genome encodes a polyprotein precursor that generates nonstructural proteins following proteolytic cleavage. Among these are the RNA-dependent RNA polymerase and other factors that form the viral replication complex in the cytosol in close association with membranes derived from the secretory pathway (22, 23). ORF2 and ORF3 encode the major and minor capsid proteins that form the viral particle. Newly developed cell culture models for human noroviruses have shed light on the cell biology of the virus, including tropism for B cells and IECs (24, 25). Norovirus and rotavirus entry in host cells is favored by binding to histo-blood group antigens (HBGAs) (26). Mutations in the *fucosyltransferase 2* (*FUT2*) gene that mediates HBGA synthesis protect against GII.4 noroviruses (27). HBGA-like molecules expressed by members of the microbiota such as *Enterobacter cloacae* bind noroviruses to facilitate infection of B cells (25).

The closely related murine norovirus (MNV) was initially discovered as an animal facility contaminant responsible for disease in immunocompromised mice, but since then it has been used as a powerful model for investigating host-virus interactions. MNV binds the cell surface protein CD300LF to infect myeloid cells and tuft cells in a strain-dependent manner (28–32). Both persistent and nonpersistent strains have been isolated. Although infection is frequently not associated with signs of illness, perhaps explaining why the virus remained undetected until 2004, some MNV strains cause intestinal disease in immunocompetent mice (33–36).

Sapoviruses are related to noroviruses and share many molecular and epidemiological features (37). Although they are an important cause of gastroenteritis, we lack an understanding of their interactions with the immune system.

3.1.3. Astrovirus. Astroviruses are also common nonenveloped +ssRNA viruses that cause diarrheal disease, most notably in children (38). Astroviruses have 3 ORFs, with ORF1a and 1b encoding nonstructural proteins and ORF2 encoding structural proteins. Although astroviruses have not been as intensely investigated as rotaviruses or noroviruses, important aspects of their biology are emerging. Both human and murine astroviruses infect mucus-secreting goblet cells (39–41). How tropism for goblet cells impacts the immune response to this virus is an exciting area of research.

3.1.4. Adenovirus. Adenoviruses are nonenveloped dsDNA viruses. There are close to 100 human adenoviruses that can cause asymptomatic infections, common cold, conjunctivitis, gastroenteritis, and life-threatening disease in immunocompromised individuals (42). Genomes vary in size, ranging from ~30 to 50 kb, and contain dozens of genes enabling intricate interactions with the host cell machinery. Adenoviruses are established enteric viruses, yet few studies address the mucosal immune response in the gut (43).

Although the viruses described above account for a large share of the hundreds of millions of cases of acute gastroenteritis around the world, in many incidents of diarrheal disease, no etiologic agent can be identified. It is likely that additional viruses contribute to gastroenteritis in humans.

3.2. Viruses That Leave the Gut to Cause Disease at Distal Sites

Numerous well-known human pathogens are picornaviruses. Although many replicate in the gut and transmit by the fecal-oral route, some are associated with extraintestinal diseases.

Picornaviruses are nonenveloped viruses with a +ssRNA genome ranging from 6.5 to 10 kb that encode polyprotein precursors that undergo autocleavage to generate individual proteins. The enteroviruses represent a genus within *Picornaviridae* and are among the most frequently detected intestinal viruses (44).

Poliovirus is an enterovirus that enters cells by binding CD155 (also known as the poliovirus receptor), found on the surface of many cell types including IECs. Physical interaction with bacteria in the gut stabilizes the virion to facilitate infection and transmission (45, 46). Poliovirus causes paralytic disease when it enters the CNS and replicates in motor neurons. The antiviral cytokine type I interferon (IFN-I) acts as a barrier for entry into the CNS (47). The inactivated poliovirus vaccine (Salk) prevents disease by inhibiting CNS infection rather than blocking intestinal replication, indicating the adaptive immune system can be mobilized to avert extraintestinal spread (48).

Enterovirus A71 (EV-71) can also cause a polio-like neurological disease, but it is more commonly a cause of hand, foot, and mouth disease (HFMD) (44). HFMD usually occurs in children and starts with a fever followed by the appearance of spots or bumps on the hands, feet, and mouth region. Symptoms resolve on their own but may lead to more serious conditions such as encephalitis. In addition to EV-71, other coxsackieviruses, especially coxsackievirus A16, cause HFMD. There are dozens of coxsackieviruses, which are divided into groups A and B, and they cause a variety of serious ailments including conjunctivitis, myocarditis, and pancreatitis. The wide tissue distribution of the coxsackievirus and adenovirus receptor, an adhesion molecule used for entry by group B coxsackieviruses and subgroup C adenoviruses, contributes to the breadth of diseases that can occur upon exposure to these viruses as well as certain adenoviruses.

Hepatitis A virus (HAV), a picornavirus, and hepatitis E virus (HEV), a nonenveloped +ssRNA virus belonging to the *Hepeviridae* family, spread by the fecal-oral route and are usually asymptomatic (49). The availability of an effective vaccine for HAV reduces the disease burden, but liver failure is not uncommon for these viruses, especially in the immunocompromised individuals chronically infected with HEV (49).

Many enteric viruses are nonenveloped, potentially because a lipid envelope is vulnerable to the harsh environment of the gastrointestinal tract, such as a shifting pH gradient and emulsifiers. However, enteric viruses can egress from cells in a nonlytic manner as clusters and acquire a pseudoenvelope in the process (50, 51). For enteroviruses, this process occurs through subversion of autophagy, a cellular pathway by which cytoplasmic material (including intracellular pathogens) is sequestered in a double-membrane vesicle termed the autophagosome. Instead of fusion with the lysosome, which would lead to degradation of the contents, viral proteins redirect the autophagosome toward the plasma membrane, leading to secretion of the inner vesicle along with its viral contents (51–55). Vesicle-bound viral clusters are transmitted more efficiently to neighboring cells and animals (51, 56).

3.3. Viruses That Reach the Gut from Another Site

The gastrointestinal tract is not the primary target of human cytomegalovirus (HCMV), human immunodeficiency virus (HIV), or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, all three viruses (and others) can infect the gut. HCMV is a large, enveloped dsDNA virus that encodes more than 200 proteins and has a broad cellular tropism allowing it to establish an infection in many organs including the gut. HCMV replicates in the nucleus without integration into the host genome and maintains a state of dormancy termed latency, in which viral genome replication and protein production are minimal or undetected, that can persist throughout the lifetime of the host (57). Reactivation of the virus from latency results in shedding of the virus in bodily fluids (e.g., saliva) and transmission through close contact. Most individuals are infected by adulthood but rarely experience disease. Colitis is one of the more common diseases

that occurs with HCMV reactivation. Damage from the immune response occurs when infection of newly recruited monocytes interferes with protective transforming growth factor beta (TGF-β) signaling (58).

HIV is the causative agent of acquired immunodeficiency syndrome (AIDS) and a major contributor of worldwide morbidity and mortality. Transmission occurs when mucosal tissue, skin abrasions, or blood is exposed to a bodily fluid from an infected individual, such as during sexual intercourse (59). As all retroviruses, HIV is enveloped and contains a dsRNA genome that, when converted to DNA through reverse transcription, integrates into the host nuclear genome to establish a lifelong infection. HIV infects and depletes $CD4^+$ T cells, fundamentally altering the immune landscape of the host, including the gut.

SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), is primarily a respiratory virus in humans with an envelope and a +ssRNA genome of approximately 30 kb. Its main receptor angiotensin-converting enzyme 2 (ACE2), which is found on the airway epithelium, is also abundant in IECs, providing a potential explanation for the widespread report of gastrointestinal symptoms during COVID-19 infections (60–62). SARS-CoV-2 RNA and proteins are routinely detected in intestinal tissue (60, 63–65), and the virus readily reproduces in intestinal organoid cultures, a 3D epithelial culture system differentiated from primary stem cells (66–68). The degree of viral replication displays orders of magnitude differences between organoid lines, which correlates with ACE2 levels in the intestinal tissue of the original donor (68), which helps explain variations in susceptibility to gut infection. Yet, few or no replication-competent viral particles are recovered from human stool specimens, suggesting that intestinal replication is not a source of transmission. Alternatively, soluble immune mediators (cytokines) and immune cells activated at another site may travel to the gut to exert their effects (69, 70). It is important to understand mechanisms of interorgan crosstalk because gastrointestinal symptoms also occur during respiratory infections by other viruses such as influenza virus (71, 72).

4. IMMUNE RESPONSE TO ENTERIC VIRUSES

4.1. The Intestinal Barrier

If a virus manages to pass through the harsh environment of the upper gastrointestinal tract, which includes digestive enzymes and the low pH of the stomach, it must then overcome a formidable chemical and physical barrier maintained by IECs (73, 74). The constant turnover of enterocytes is an important feature of the epithelial barrier because infected cells are shed and replaced, which stymies viral infections (15). For example, segmented filamentous bacteria in the gut microbiota protects mice from rotavirus infection and norovirus-induced inflammation by accelerating epithelial turnover (75, 76).

Mucus is a hydrogel generated from cross-linking highly glycosylated mucin proteins, mainly mucin-2 in the gut. Mucus layers may impede the diffusion of virions (77), impair entry of some viruses such as rotavirus (78, 79), and trap and concentrate antimicrobial factors and immunoglobulin A (IgA). Antimicrobial factors include α-defensins, which in addition to disrupting bacterial membranes promote or impair cell entry in a virus strain–dependent manner (80–82) (**Figure 2**; **Supplemental Table 1**). Interestingly, defensins can promote the antibody response to adenovirus (83).

Supplemental Material >

Antibodies secreted by differentiated B cells (e.g., plasma cells), especially dimeric IgA, are transferred to the lumen by transcytosis through IECs and mediate protection via agglutination and exclusion from the epithelial surface (84) (**Figure 2**). Individuals impaired in antibody production, such as common variable immunodeficiency and IgA deficiency, are susceptible to recurrent enteric viral infections (85). Mother's milk, which contains IgA and other factors involved in

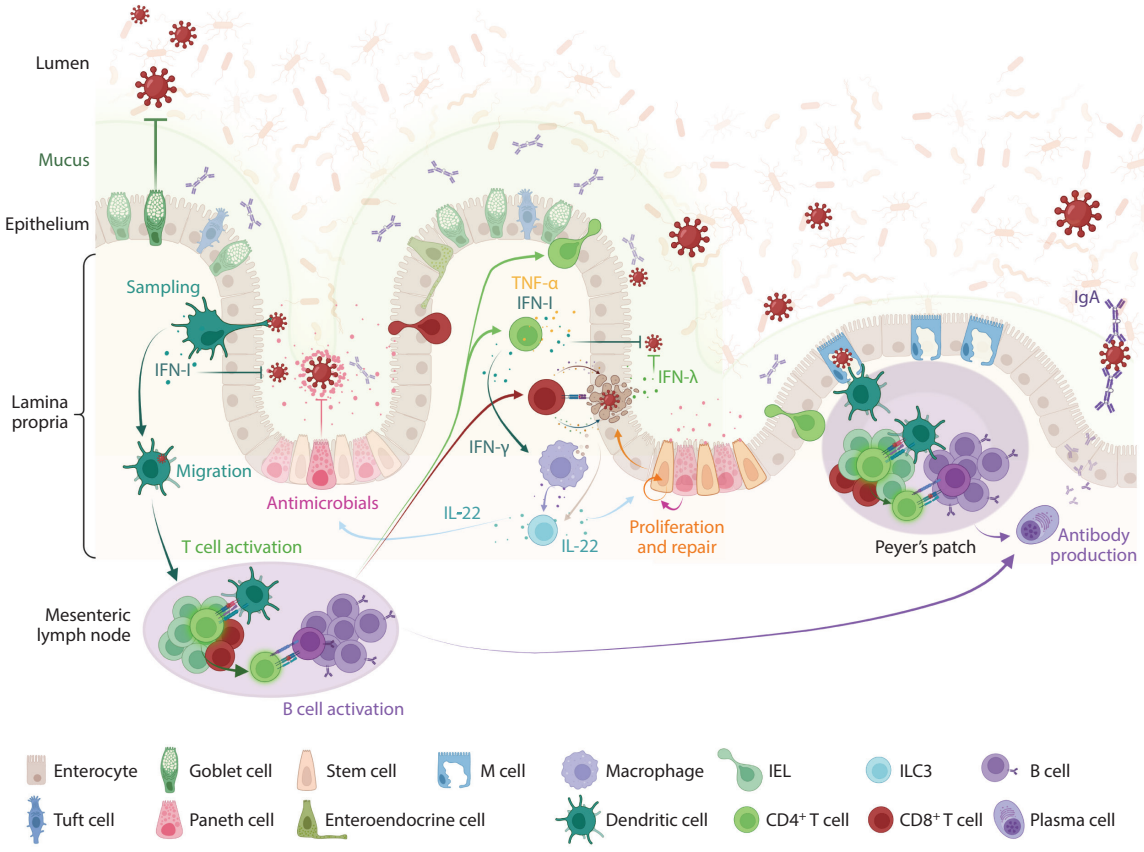

Figure 2

Overview of the immune response to viruses in the gut. Enteric viruses that infect intestinal epithelial cells and/or immune cells lead to activation of viral nucleic acid sensors that trigger secretion of type I and III IFNs (IFN-I, IFN-λ) that induce antiviral gene expression in infected and neighboring cells. DCs and macrophages engulf viruses or infected cells. M cells overlaying Peyer's patches in the small intestine facilitate sampling of viruses in the lumen. In the Peyer's patches or upon migration to the mesenteric lymph nodes, DCs presenting viral antigens activate $CD4^+$ and $CD8^+$ T cells that migrate to the lamina propria and epithelium. $CD4^+$ T cells coordinate multicellular immune responses, including activation of other cells through IFN-γ and TNF-α and promoting the differentiation of B cells into plasma cells that produce antibodies including IgA that are transferred across the epithelium. $CD8^+$ T cells induce apoptosis of infected cells. Macrophages phagocytose and eliminate apoptotic cells, and activate ILC3s, leading to the production of IL-22, which increases antimicrobial factors and proliferation of stem cells to replace dead epithelial cells. Abbreviations: DC, dendritic cell; IEL, intraepithelial lymphocyte; IFN, interferon; IgA, immunoglobulin A; IL-22, interleukin 22; ILC3, group 3 innate lymphoid cells; M cell, microfold cell; TNF-α, tumor necrosis factor-α. Figure adapted from Reference 6 (CC BY-NC-SA 4.0) and images created with BioRender.com.

immunity, impacts the gut virome of infants (4). IgA secretion in the maternal milk can be induced by transmission of rotavirus, MNV, and astroviruses from infected infant mice to their mothers' mammary glands through backflow during suckling (11). Therefore, IgA and other antibodies collaborate with a multitude of secreted products to form a chemical barrier that coats the epithelial layer.

4.2. Sensing and Induction of Inflammatory Mediators

Viruses that make it past the mucus and antimicrobial barrier to invade cells are subject to recognition by pattern recognition receptors (PRRs) that initiate the innate immune response.

PRRs activate signaling adaptors upstream of the transcription factors nuclear factor kappa B (NF-κB), interferon regulatory factor (IRF) 3, and IRF7 to induce expression of genes involved in host defense, including IFNs. PRRs involved in antiviral immunity detect nucleic acids from viral genomes or replication intermediates, which are distinguished from host nucleic acids by structural properties and subcellular location (86) (**Figure 3**). The presence of nucleic acids in endosomal compartments is sensed by PRRs belonging to the toll-like receptor (TLR) family that signal through TRIF [TIR (toll/interleukin-1 receptor) domain-containing adaptor protein inducing interferon beta] and/or MyD88 (myeloid differentiation primary-response gene 88). These PRRs have a restricted expression pattern in the gut, mainly in the lamina propria (87). TLR3 detects dsRNA while TLR8 and TLR7 detect guanosine (G)- and uridine (U)-rich ssRNA and dsRNA. TLR9 senses cytosine-guanine dinucleotide (CpG) motifs in dsDNA.

In the cytosol, short and long dsRNA are detected by retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), respectively, that signal through the adaptor mitochondrial antiviral-signaling protein (MAVS). RIG-I also senses uncapped 5′-triphosphate RNA. DEXD/H box helicase family members such as DHX15, poly(ADP-ribose) polymerase 9 (PARP9), and protein kinase R (PKR) also sense cytosolic RNA while DNA is detected by the cyclic GMP–AMP synthase (cGAS) stimulator of interferon gene (STING) pathway. Nucleotide oligomerization domain–like receptors (NLRs) are activated by a variety of products derived from pathogens and indicators of cellular damage such as cytosolic nucleic acids and mitochondrial injury. Depending on the trigger, NLRs induce IFN via MAVS or trigger inflammasomes, a multimeric complex that activates the cysteine protease caspase-1, which cleaves to generate active forms of the cytokines interleukin (IL)-1β and IL-18 and the pore-forming molecule gasdermin D. The release of cytokines through the gasdermin D pore and subsequent inflammatory cell death (pyroptosis) restrict virus replication and promote adaptive immunity. Although traditionally examined in the context of bacterial infections, emerging literature shows that NLRs bind adaptors that recognize viruses in IECs. NLRP6 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-6) in complex with the RNA binding protein DHX15 is a sensor of the picornavirus encephalomyocarditis virus, norovirus, reovirus, and rotavirus leading to IFN production while rotavirus can also be sensed by NLRP9b through DHX9 leading to inflammasome activation (88–90) (**Supplemental Table 1**).

Supplemental Material >

The two major types of IFNs induced by the above nucleic acid sensors are IFN-α/β (type I IFN) and IFN-λ (type III IFN). Although they bind distinct receptors, both signal through the Janus kinase (JAK) family of kinases and their target transcription factors signal transducers and activators of transcription 1 (STAT1) and STAT2 to induce a similar set of interferon stimulated genes (ISGs) that inhibit viruses through a multitude of mechanisms including cleavage of viral RNA. However, there is currently a lack of information on how ISGs inhibit enteric viral infections. IFN-I and its receptor interferon-α/β receptor (IFNAR) are ubiquitous while IFN-λ is produced by epithelial cells and its receptor interferon λ receptor (IFNLR) is on neutrophils and epithelial cells. IFN-γ (type II IFN) has distinct activities with a separate mechanism by which it is regulated. IFN-γ is produced by T cells and natural killer (NK) cells to mediate communication between these lymphoid cells and other cells such as macrophages. In general, IFN-λ restricts local replication of enteric viruses such as rotavirus in IECs, while IFN-I and IFN-γ prevent replication in immune cells and extraintestinal dissemination (91–96) (**Supplemental Table 1**).

Other cytokines downstream of viral sensing contribute to host defense, such as tumor necrosis factor-α (TNF-α), IL-1, IL-6, IL-18, and IL-22 (**Supplemental Table 1**). The coordinated action of multiple cytokines is exemplified by responses to rotavirus infection. In adult mice, IL-18 promotes death of rotavirus-infected cells and synergizes with IL-22 produced by group 3 innate lymphoid cells (ILC3s) that induce IEC proliferation to accelerate turnover and viral elimination

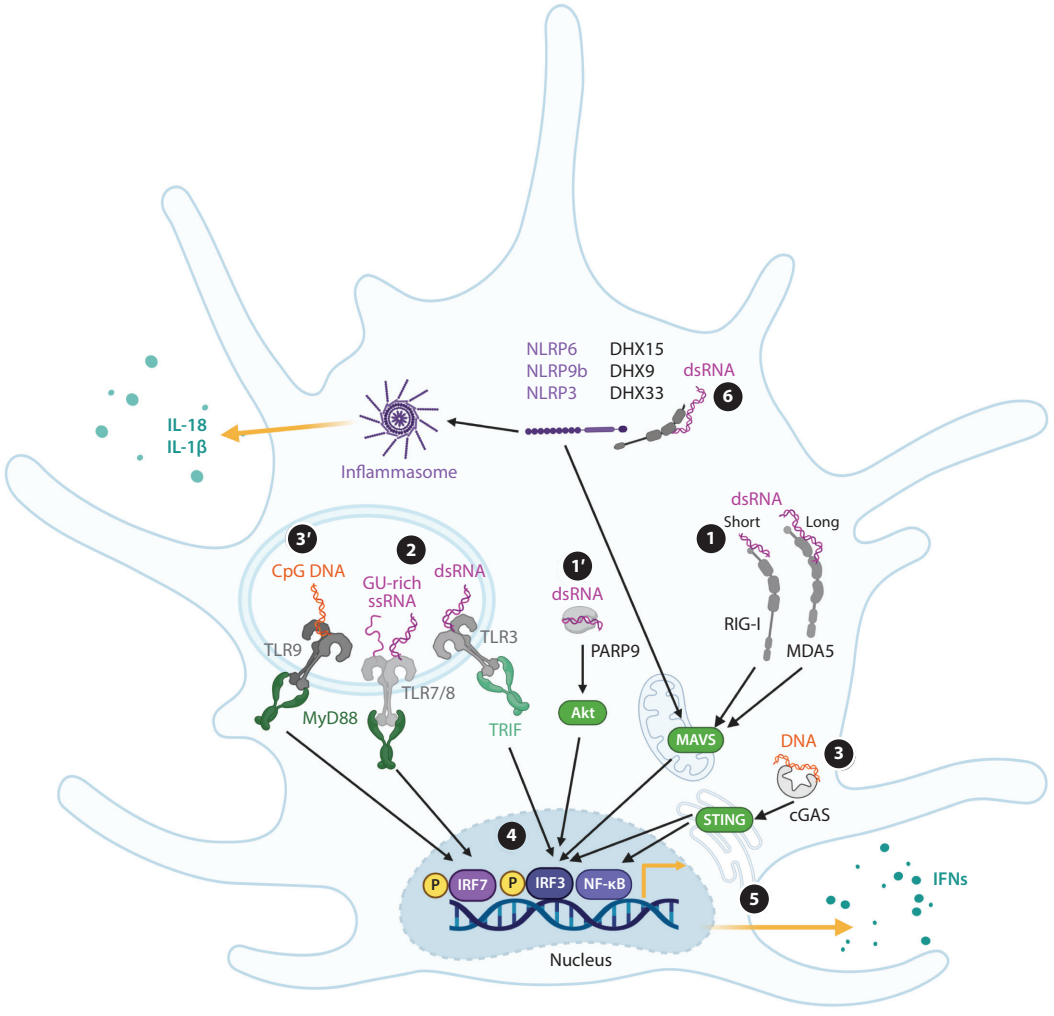

Figure 3

Nucleic acid sensors induce antiviral cytokine production. Viral ssRNA or dsRNA generated during rotavirus, reovirus, and norovirus infections is sensed by RIG-I, MDA5, or PARP9 in the cytosol (①) or by TLR3 or TLR7/8 in the endosome (②). DNA viruses such as adenoviruses are sensed via TLR9 or cGAS (③). Activation of these receptors initiates different signaling cascades converging in phosphorylation of IRF3 and IRF7 or activation of NF-κB (④), which induces expression of effector genes such as IFNs (⑤). dsRNA bound to DHX15, DHX9, or DHX33 also activate NLRP6, NLRP9b, or NLRP3 to induce IFNs through MAVS or IL-18 and IL-1β release through the inflammasome (⑥). Abbreviations: Akt, protein kinase B; cGAS, cyclic GMP–AMP synthase; CpG, cytosine-guanine dinucleotide; dsRNA, double-stranded RNA; GU, guanosine, uridine; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated protein 5; MyD88, myeloid differentiation primary-response gene 88; NF-κB, nuclear factor kappa B; NLRP, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing; P, phosphorylated protein; PARP9, poly(ADP-ribose) polymerase 9; RIG-I, retinoic acid-inducible gene I; ssRNA, single-stranded RNA; STING, stimulator of interferon gene; TLR, toll-like receptor; TRIF, toll/interleukin-1 receptor domain-containing adaptor protein inducing interferon beta. Figure adapted from Reference 194 (CC BY 4.0) and images created with BioRender.com.

(97). In this context, cytokine production is dependent not on rotavirus sensing but on sensing of bacterial flagellin from the microbiota by TLR5 and NLR family CARD domain-containing protein 4 (NLRC4) (97–99). In neonates, IL-22 production by ILC3s is mediated by infected IECs that produce IL-1α, which synergizes with IFN-λ to increase STAT1 signaling to restrict rotavirus replication (100).

4.3. B and T Cell Response

B and T cells are lymphocytes and the main effectors of the adaptive immune response, so called because this branch of immunity adapts to the nuances of a specific infectious agent. Dendritic cells (DCs) and macrophages found throughout the gut, including Peyer's patches, function as antigen-presenting cells (APCs) that carry viral antigens to draining lymph nodes for initiating B and T cell responses, especially the T helper type 1 (Th1) response characterized by IFN-γ and TNF-α production by $CD4^+$ T cells (T helper cells) and $CD8^+$ T cells (cytotoxic T lymphocytes) (**Figure 2**). Viruses such as norovirus and reovirus can exploit these mechanisms to bypass the epithelium and infect APCs by using Peyer's patches as a portal of entry (101). APCs select for $CD4^+$ and $CD8^+$ T cells that recognize viral protein antigens presented on MHC-II and MHC-I molecules, respectively. $CD4^+$ T cells participate in activation of $CD8^+$ T cells that kill infected cells by releasing cytotoxic molecules and B cells that differentiate into antibody-secreting plasma cells. Experiments with rotavirus show that the timely reduction of viral burden in the gut requires the coordination of all these responses (102–104) (**Supplemental Table 1**). After the infection is resolved, a small proportion of the antigen-specific T and B cells remain and rapidly expand in a memory response upon re-encountering the same viral antigens, allowing for a quicker and more effective response upon subsequent exposure. Vaccines prepare the immune system for this superior recall response by mimicking this process.

Supplemental Material >

As mentioned earlier, IgA has a central role in protecting the mucosa as part of the chemical defense structure and is produced copiously by plasma cells in the gastrointestinal tract. Other antibody isotypes such as IgG are likely important in defense against enteric viruses because IgG administration is sufficient to mediate clearance of MNV in chronically infected mice, and protection against GII-4 norovirus is associated with high IgG titers (105, 106).

T cells in the lamina propria have the typical CD8αβ heterodimer, while those within the small intestinal epithelium are distinguished by CD8αα homodimers on their surface and collectively referred to as intraepithelial lymphocytes (IELs). IELs can additionally express CD4 or CD8αβ, and some recognizing self-antigens bear either T cell receptor (TCR) αβ or the unconventional TCRγδ chains (107). IELs are maintained locally in an activated yet resting state. They produce inflammatory cytokines such as IFN-γ, TNF-α, IFN-I, and IFN-λ in response to MNV, and TCRαβ and CD8αβ IELs produce perforin and granzyme to lyse lymphocytic choriomeningitis virus (LCMV)-infected cells (108–110). Therefore, IELs probably play a role in many enteric viral infections, but the division of labor during enteric viral infections between lamina propria T cells and IELs requires clarification.

T cell responses are influenced by the microbiota or the presence of other infectious agents. As an example, coinfection with the parasitic helminth *Trichinella spiralis* increases the burden of a nonpersistent strain of MNV by reducing the number of virus-specific $CD8^+$ and $CD4^+$ T cells and impairs their production of IFN-γ and TNF-α (111). In an example of cross-protection, a distinct population of $CD4^+$ T cells recruited in response to MNV infection mediates clearance of adenovirus (112). Although $CD4^+$ and $CD8^+$ T cells are induced and required to clear nonpersistent strains of MNV, other strains have evolved ways to evade the response (113–115). Mechanisms that contribute to this immune evasion are discussed below.

Finally, T cell activation can have deleterious effects during chronic infections or when their activity is not properly counterbalanced by regulatory T cells (Tregs) that quell inflammation. IFN-I and $CD8^+$ T cell activation during persistent LCMV infection increases intestinal barrier permeability and susceptibility to colitis (116). Tregs are initially lost during LCMV infection, but rapid Treg expansion from an existing pool of T cells ensues to prevent an inflammatory response to the microbiota (117). However, Treg-mediated inhibition of $CD8^+$ T cells or induction of senescence of $CD8^+$ T cells facilitates LCMV and HIV persistence, and Tregs contribute to the poor T cell induction in rotavirus-infected neonates (118, 119).

5. IMMUNOMODULATION BY ENTERIC VIRUSES

5.1. Mechanisms of Immune Antagonism and Subversion

Enteric viruses evade the above immune responses through various mechanisms to establish a productive infection. These mechanisms include cleavage of host molecules (e.g., reovirus σ1 protein and mucus), conformation changes of the viral capsid to avoid neutralization by antibodies and antimicrobials (e.g., enterotropic adenoviruses), inhibition of immune signaling pathways (e.g., JAK-STAT signaling inhibition by enteroviruses), disruption of antigen presentation (e.g., through rearrangement of membranes during coxsackievirus B3 infection), and evocation of anti-inflammatory pathways (e.g., IL-10 production in response to lipopolysaccharide bound to mouse mammary tumor virus) (120–125). Here we use MNV as an example of how individual viruses evade immunity through multiple mechanisms to establish infections in the gut.

MNV inhibits translation of ISG mRNA and possesses a fourth ORF not present in human noroviruses, which encodes virulence factor 1 that reduces IFN-I levels by inhibiting antiviral signaling (126–128). Antigen presentation is compromised due to reduced MHC-I levels (129), decreased maturation of APCs, and blunted B cell–dependent T cell responses (113, 130). MNV also coopts cell death to promote cell-to-cell spread. In the absence of IFN signaling, VP1 from the nonpersistent MNV CW3 strain promotes extraintestinal dissemination by mediating lytic death of infected cells, which recruits myeloid cells that serve as a continuous source of target cells for additional rounds of infection (131) (**Figure 4**). Persistent strains such as MNV CR6 display additional adaptations to facilitate prolonged infection. Nonstructural protein 1 (NS1) from persistent strains increases caspase activity to cause IEC death, thereby spreading virus to neighboring cells (132). NS1 is also secreted and blocks IFN-λ signaling in tuft cells, and administration of IFN-λ overcomes this blockade to cure mice of infection (29, 133–136) (**Figure 4**). Tuft cells serve as a reservoir for persistent MNV strains, potentially by shielding the virus from T cell recognition (28, 137). Also, the bacterial microbiota enables persistent MNV infection by decreasing IFN-λ signaling (28, 29, 138). For nonpersistent strains of MNV, bacteria-transformed bile acids induce IFN-λ in the proximal intestine, explaining the preference of MNV for more distal parts of the gut where bile acid receptors are expressed at lower levels (139). As discussed below, this modulation of immune responses by MNV and other enteric viruses has consequences for the host beyond controlling viral burden.

5.2. Beneficial Immunomodulation by Enteric Viruses

Since the seminal observation that treatment of mice with antibiotics inhibits immune responses that protect against chemically induced intestinal injury (140), there has been an explosion of studies demonstrating how bacterial products from the microbiota promote development of the immune system. Experiments with MNV indicate that beneficial cues for the immune system can also be provided by enteric viruses. Persistent MNV infection reverses intestinal and immune

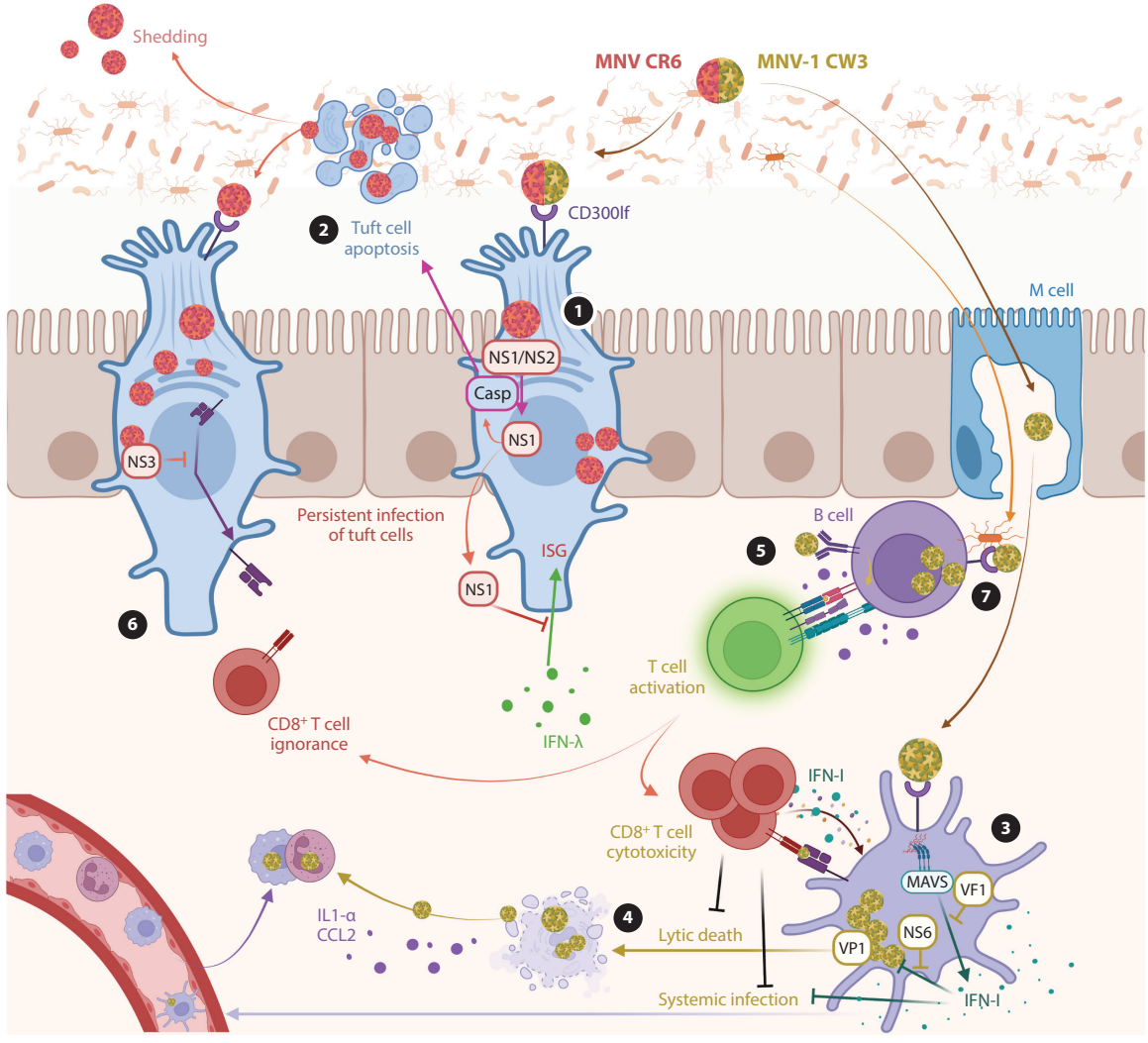

Figure 4

MNV strain-specific immune antagonism mechanisms dictate clearance versus persistence. MNV CR6 and CW3 are representative persistent and nonpersistent strains that bind CD300lf to infect tuft cells and myeloid cells, respectively. (①) NS1/2 from MNV CR6 is cleaved by caspase 3 to generate NS1, which contributes to viral persistence by interfering with IFN-λ signaling. (②) NS1 also promotes CR6 spread to neighboring tuft cells and fecal shedding by activating caspases that induce apoptosis. (③) MNV CW3 exploits M cells to cross the epithelial barrier and infect APCs in Peyer's patches. Recognition of MNV by MDA5 inhibits viral replication through IFN-I, but VF1 reduction of IFN-I production and NS6 blockade of ISG mRNA translation allows systemic infection to occur in absence of adaptive immunity. (④) CW3 VP1 induces lytic cell death in infected macrophages and DCs, leading to production of IL1-α and CCL2 that recruit neutrophils and monocytes that can be infected to perpetuate the viral life cycle. (⑤) B cells function as APCs to promote T cell responses against MNV, but variations in VP1 sequence among strains limit cross-neutralization by antibodies. Compared with CW3, CR6 infection of tuft cells evokes a weaker T cell response associated with reduced MHC-II levels and inflammatory cytokine production. (⑥) CR6 NS3 interferes with MHC-I levels. These mechanisms contribute to the failure of T cells to eliminate the CR6 reservoir. (⑦) Bacteria expressing HBGA-like molecules favor MNV infection, especially B cells. Abbreviations: APC, antigen-presenting cell; Casp, caspase; CCL2, chemokine (C-C motif) ligand 2; DC, dendritic cell; HBGA, histo-blood group antigen; IFN, interferon; IL, interleukin; ISG, interferon stimulated gene; M cell, microfold cell; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated protein 5; MNV, murine norovirus; mRNA, messenger RNA; NS, nonstructural protein; VF1, virulence factor 1; VP1, viral protein 1. Figure adapted from images created with BioRender.com.

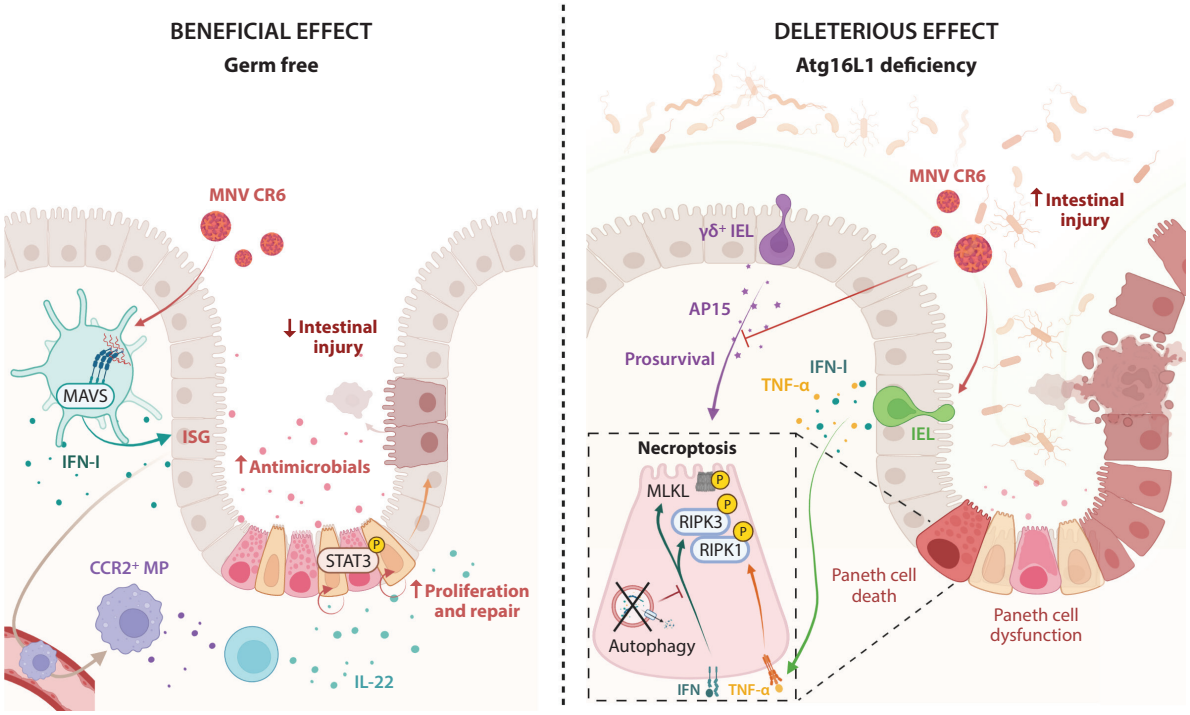

Figure 5

Host genetics determine outcome of MNV CR6 infection. (*Left*) Germ-free mice are susceptible to intestinal injury due to the absence of wound healing signals from the microbiota. MNV CR6 is sufficient to restore resilience to intestinal injury. CCR2$^+$ monocytes are recruited to the gut following MAVS-dependent IFN-I production that acts on IECs to induce ISG expression. Myeloid cells including recruited monocytes activate ILC3s that produce IL-22, which induces STAT3 phosphorylation in IECs to increase repair and antimicrobials from Paneth cells. (*Right*) MNV triggers disease in the absence of *ATG16L1*, an autophagy gene associated with IBD. Although API5 from γδ IELs protects ATG16L1-deficient IECs, MNV CR6 infection inhibits API5 secretion to induce Paneth cell necroptosis. In this form of programmed necrosis, exaggerated ISG expression due to ATG16L1 deficiency increases sensitivity to TNF-α produced by IELs, leading to a phosphorylation cascade through RIPK1 and RIPK3, resulting in formation of MLKL pores. In such a manner, virus and genetic susceptibility combine by skewing toward a proinflammatory environment and increasing sensitivity to damage. Abbreviations: API5, apoptosis inhibitor 5; CCR2, CC-chemokine-receptor 2; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; IEL, intraepithelial lymphocyte; IFN, interferon; IL, interleukin; ISG, interferon stimulated gene; MAVS, mitochondrial antiviral-signaling protein; MLKL, mixed-lineage kinase domain-like; MNV, murine norovirus; MP, myogenic progenitor; P, phosphorylated protein; RIPK, receptor interacting protein kinase; STAT3, signal transducers and activators of transcription 3; TNF-α; tumor necrosis factor-α. Figure adapted from images created with BioRender.com.

abnormalities in germ-free mice and antibiotics-treated mice, including susceptibility to chemically and bacterially induced injury to the gut. This restoration of a robust injury response is mediated by the IFN-I response due to MAVS activation and IL-22 production by ILC3s (141, 142) (**Figure 5**). This mechanism may be important in situations in which the bacterial microbiota is perturbed or underdeveloped, such as during early childhood. IL-22 induced by MNV protects against vancomycin-resistant *Enterococcus faecium* colonization in a model of hospital-acquired infection (143) and prevents lethal infection of juvenile mice by *Citrobacter rodentium*, a Gram-negative pathogen related to *E. coli* (141). Comprehensive immune profiling of germ-free mice mono-associated with a panel of 10 enteric viruses revealed a diversity of effects on the intestinal immune system reminiscent of studies documenting how individual bacterial species promote immune development. Although each virus induced a unique immune reaction, IL-22

induction and the Th1 response were common to most of them (144). While all the viruses including nonpersistent ones induced an immune signature, all except one caused disease. These findings indicate that asymptomatic infections are not immunologically silent and that enteric viruses contribute to the immune landscape of the host.

Further evidence that commensal viruses provide homeostatic cues comes from experiments in which mice receive a cocktail of antiviral drugs. They reveal that activation of RIG-I induces IL-15 from APCs to maintain IELs, while TLR3 and TLR7 induce IFN-β from plasmacytoid DCs, and both pathways protect the intestinal barrier (145, 146). Also, IFN-λ induction linked to the presence of viruses protects against colitis by reducing reactive oxygen species production and degranulation of neutrophils (147). The IFN-I response to murine cytomegalovirus, a herpesvirus commonly detected in feral mice, induces macrophages to produce factors that increase IEC proliferation and promote wound healing (148). A strain of another widely detected mouse virus, murine astrovirus, protects immunocompromised mice from MNV and rotavirus infection by inducing IFN-λ (149). Also, astrovirus infection of goblet cells alters the mucus layer so as to increase resistance to enteropathogenic *E. coli* colonization (39). Finally, MNV decreases bacterial load and lung inflammation during *Pseudomonas aeruginosa* infection, indicating that the presence of enteric viruses has extraintestinal benefits (150).

5.3. Contribution of Enteric Viruses to Inflammatory Diseases

Perturbation of the gut virome is observed with IBD, celiac disease, colorectal cancer, and enteric graft-versus-host disease (5, 151–157). Inflammation is associated with shifts in the virome composition or reflects a more traditional pathogenic role for individual viruses such as noroviruses. Viruses isolated from the colon of non-IBD individuals elicit an anti-inflammatory response from human macrophages and protect mice from colitis. In contrast, the viral fraction of colonic specimens from IBD patients, which is enriched for enterovirus B, a picornavirus, increased inflammation in vitro and in vivo (157). Additionally, MDA5 loss-of-function variants are associated with the development of IBD (158), and the presence of these variants impaired barrier integrity in an in vitro assay when human IECs were exposed to enteric viruses derived from IBD specimens (157). These findings are reminiscent of the MAVS-dependent protection conferred by MNV infection of mice (141).

Genetic susceptibility determines whether immune responses to enteric viruses are beneficial or adverse. The Th1 response to MNV CR6 infection, an otherwise beneficial virus, exacerbates disease in several models of IBD including mice with mutations in *Atg16L1* (159–161). ATG16L1 mediates autophagy, which has several functions during infectious disease including promoting cellular homeostasis and viability (162). A coding variant of *ATG16L1* is a risk factor for Crohn's disease, a subset of IBD. Patients and mice carrying *Atg16L1* variants exhibit fewer Paneth cells with functional granules (163). In mice, these Paneth cell defects are dependent on persistent MNV infection and Th1 cytokines (161). MNV infection inhibits secretion of the prosurvival factor API5 by γδ IELs, which lowers the threshold for TNF-α to induce necrotic cell death (necroptosis) of Paneth cells. Specifically, exaggerated ISG expression due to ATG16L1 deficiency increases sensitivity to TNF-α, leading to a phosphorylation cascade of receptor interacting protein kinase 1 (RIPK1) and RIPK3, eventually resulting in formation of mixed-lineage kinase domain-like pores that cause the cells to lyse (109, 164, 165) (**Figure 5**). Although it remains to be determined whether human noroviruses enriched in Crohn's disease patients are a cause or consequence of the disorder (156), these findings with MNV elucidate a specific set of molecular events associated with enteric viral infection that cause inflammatory damage in susceptible individuals.

SARS-CoV-2 mediates similar Paneth cell abnormalities but in absence of *Atg16L1* mutation (70). Intestinal abnormalities in mice were associated with barrier dysfunction and bacterial

microbiota dysbiosis such as those observed in COVID-19 patients with bacterial bloodstream infections. Here, SARS-CoV-2 was not detected in the intestine of infected mice (70), suggesting the systemic inflammatory response to the virus is responsible as it was observed in another study (69). Loss of $CD4^+$ T cells during HIV infection is associated with an altered microbiome and virome and microbial translocation (166–169). AIDS caused by simian immunodeficiency virus infection of macaques also implicates a role for altered α-defensin secretion by Paneth cells and IL-1β-mediated disruption of epithelial tight junctions (170–172).

Celiac disease is an autoimmune disorder characterized by a Th1 response to dietary gluten. This disease mostly happens in individuals carrying human leukocyte antigen DQ2 or DQ8 alleles, but as for Crohn's disease, genetic variation is not sufficient. Rotavirus infections and antibodies against reovirus are associated with disease development (173, 174). In mice, the IFN-I response to MNV CW3 and reovirus TL1 (but not MNV CR6 or reovirus T3D-RV), amplified by NK cells recruited to the mesenteric lymph nodes, suppresses Treg responses while concurrently eliciting IL-12 from DCs carrying dietary antigens that induce differentiation of Th1 cells (174–176).

Viruses are also implicated in type 1 diabetes (T1D) in which T cells destroy pancreatic islet β cells, leading to insulin deficiency (177). Chronic viral infections with enterovirus and rotavirus are associated with T1D, and enteroviruses have been detected in pancreatic islets (178–180). One proposed mechanism is that enteroviruses induce microRNA synthesis in infected β cells that target genes involved in T1D susceptibility (181). In the nonobese diabetic (NOD) mouse model, coxsackievirus or rotavirus infection accelerates T1D development through bystander activation of existing autoreactive T cells by IFN-I production downstream of TLR7 in plasmacytoid DCs (182–184). IFN-I induced by viral infection also acts directly on β cells to increase MHC-I expression, impair insulin secretion, and induce cell death (185, 186). Enterovirus infection of the thymus could impair T cell development and increase autoreactive T cells (187). By contrast, infection of NOD mice with the persistent strain MNV-4 prior to disease development is protective by favoring Treg activation over inflammatory T cells, highlighting again that outcomes are virus and timing specific (188). If results obtained in animal models reflect disease trajectories in humans, epidemiological studies may need to integrate viral strain information, timing, and host genetics to make meaningful associations.

6. CONCLUSION

Enteric viruses display remarkable adaptations that allow successful propagation in their mammalian hosts, sometimes leading to life-threatening diseases. Addressing this enormous toll on human health requires continued research efforts and the design of new antivirals and vaccines. Still, infections by enteric viruses are frequently asymptomatic in immunocompetent individuals, indicating the existence of mechanisms that allow us to tolerate their presence. An improved understanding of how coexistence is achieved may reveal alternate therapeutic strategies, such as biologics that target immune mediators involved in tissue injury and repair.

More recent findings suggest that enteric viruses cause long-term consequences that can be beneficial or detrimental. There is emerging evidence that commensal viruses in the gut provide homeostatic cues for the immune system and that diseases occur when genetic susceptibility or expansion of inflammatory viruses disrupts this symbiotic relationship. This paradigm, in which the composition and dynamics of the virome affect host physiology, is reminiscent of findings from the microbiome field. Given the examples discussed in this review demonstrating that viruses interact with bacteria in the gut, it may be useful to consider enteric viruses as a component of the microbiota that functions alongside bacteria, fungi, and other microbial agents.

Advances in human immunology will facilitate the identification of host factors that determine outcomes of enteric virus infections. Few studies have examined sex as a variable in this context

despite known effects of sex chromosomes and hormones in immunity. Analysis of human jejunum biopsies revealed a higher proportion of TNF-α, IL-17, or TGF-β producing $CD4^+$ T cells, IL-1β levels, and expression of genes associated with regenerative pathways in adult females (189), which may explain the superior clearance of coxsackievirus B3 in female mice compared with their male counterparts (190). The use of mouse models, including a recently described neonatal norovirus infection model (35), will also clarify age-dependent vulnerabilities to disease caused by enteric viruses.

As the sensitivity of techniques for detecting viruses improves, along with reduction in costs, there will likely be more instances in which the gut virome is associated with health outcomes. In addition to inflammatory diseases discussed earlier, enteric viruses may shape efficacy of cancer therapies and vaccines. For instance, the presence of enteroviruses impairs seroconversion following rotavirus vaccination in Ghanian and Bangladeshi infants (191, 192). The studies that describe important associations between enteric viruses and human physiology will, in turn, generate hypotheses that can be tested in experimental systems. Given that the immune response to many enteric viruses remains to be fully characterized, there is tremendous opportunity to elucidate novel mechanisms and outcomes of virus-host interactions in the gut.

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