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Immunity to enteric viruses

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SUMMARY

Pathogenic enteric viruses are a major cause of morbidity and mortality, particularly among children in developing countries. The host response to enteric viruses occurs primarily within the mucosa, where the intestinal immune system must balance protection against pathogens with tissue protection and tolerance to harmless commensal bacteria and food. Here, we summarize current knowledge in natural immunity to enteric viruses, highlighting specialized features of the intestinal immune system. We further discuss how knowledge of intestinal anti-viral mechanisms can be translated into vaccine development with particular focus on immunization in the oral route. Research reveals that the intestine is a complex interface between enteric viruses and the host where environmental factors influence susceptibility and immunity to infection, while viral infections can have lasting implications for host health. A deeper mechanistic understanding of enteric anti-viral immunity with this broader context can ultimately lead to better vaccines for existing and emerging viruses.

INTRODUCTION

Pathogenic enteric viruses, characterized by fecal-oral transmission and intestinal replication, are a major cause of worldwide morbidity and mortality. Localized intestinal infection by enteric viruses such as adenovirus-A, -F, and -G (*Adenoviridae*), norovirus (*Caliciviridae*), astrovirus (*Astroviridae*), sapovirus (*Caliciviridae*), and rotavirus (*Reoviridae*) cause gastroenteritis characterized by tissue inflammation, disruption of the epithelial barrier, malabsorption, and diarrhea (Banyai et al., 2018; Liu et al., 2016). Rotavirus is the primary pathogen responsible for diarrheal mortality, causing >200,000 deaths and millions of hospitalizations each year, while adenovirus and norovirus are responsible for an additional 100,000 annual deaths (GBD Diarrhoeal Disease Collaborators, 2018; Hallowell et al., 2021). Hepatoviruses and enteroviruses (*Picornaviridae*), such as hepatitis A, poliovirus, and coxsackievirus, infect via the oral route but cause few gastrointestinal symptoms and result in clinical disease only after dissemination to another site. Enteric viruses have diverse genetic composition, cellular tropism, and pathophysiology, though all 16 human viruses known to be transmitted in oral route are non-enveloped, likely because a lipid membrane would be disrupted in the harsh environment

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DECLARATION OF INTERESTS

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of the digestive tract (Bushman et al., 2019). Key features of major enteric viruses are summarized in Figure 1.

The host response to enteric viruses occurs primarily within the intestinal mucosa, which contains a single layer of epithelial cells, connective tissue beneath termed the lamina propria, and an underlying layer of muscle. Most immune cells are found in the epithelium and lamina propria, which each form distinct immune compartments. Induction of immune responses to intestinal antigen occurs in gut-draining lymph nodes and gut-associated lymphoid tissues such as Peyer's patches (Mowat and Agace, 2014). The majority of immune stimulation in the intestine comes from commensal microbes and food. The intestinal immune system must balance immunological tolerance to these harmless entities with protection against pathogens. Dysregulated immune responses may lead to tissue damage, inflammatory bowel disease, or food allergy, and accordingly the intestinal immune system is set in a default state of tolerance. Although these immune-suppressive pathways are mainly targeted at extracellular antigen, there is a high threshold in general for immune activation in the gut. Enteric pathogens and vaccines that enter in the oral route must therefore provide a higher level of stimulation to overcome tolerance, providing important context for the nature of effective antiviral immunity in the gut (Faria et al., 2017; Zhou and Sonnenberg, 2018). Another key concept for antiviral immunity is that viruses have evolved strategies to evade every step of the immune response, while the immune system compensates with redundant mechanisms for viral detection and control. This tradeoff is made evident by the existence of multiple converging innate immune pathways for viral detection as well as the multi-faceted adaptive immune response.

During viral infection, epithelial and innate cells detect the breach via cytosolic and membrane pattern recognition receptors. A cascade of signaling pathways is activated within the cells that in turn activates the production of inflammatory mediators such as type I and III interferons (IFN-α/β/λ), interleukin (IL)-6, IL-1β, IL-18, and tumor necrosis factor alpha (TNF-α) (Figure 2A). These interferons and cytokines alarm the surrounding cells by inducing the activation of intrinsic anti-viral programs and the activation of endothelial cells to facilitate the recruitment of leukocytes. Dendritic cells (DCs) in the lamina propria that have taken up viral particles migrate to the mesenteric lymph nodes and present processed viral antigens to virus-specific T cells via major histocompatibility complex (MHC) class I and II molecules. Subsequently, virus-specific T cells differentiate into memory and effector subtypes with anti-viral properties and upregulate gut homing receptors such as α4β7 and CCR9 to migrate to the intestinal tissue (Figure 2B). The recruited intestinal virus-specific T cells can directly eliminate virus-infected cells via granzyme/perforin- or cytokine-mediated cytotoxicity (Figure 2C). Simultaneously, viral antigen capture and presentation within specialized immune structures in the intestinal tissue called Peyer's patches results in the activation and differentiation of virus-specific B cells, generally in a T cell-dependent manner. The activated B cells differentiate into plasma cells that produce large amounts of virus-specific secretory immunoglobin A (IgA) antibodies that are translocated to the lumen where they can neutralize virus (Figure 2D). T cells and plasma cells activated during a primary viral infection can establish permanent tissue residence in the gut or migrate to the bone marrow and mount rapid responses upon secondary infection. Thus, the intestinal

immune system can quickly detect and clear viruses through innate mechanisms, as well as establish long-term antigen-specific protective immunity through adaptive mechanisms.

In this review, we will summarize current knowledge of natural immunity to enteric viruses and how this knowledge is being translated into vaccine development, highlighting specialized features of intestinal immunity. Human studies in this field have been hindered by difficulty in accessing mucosal tissues, necessitating the use of gut-homing immune responses in peripheral blood as the main readout for mucosal immunity. Accordingly, we will discuss findings from human studies where possible while also highlighting functional and mechanistic studies from mice.

INNATE ANTIVIRAL RESPONSES

The intestinal epithelium and associated mucus layer form a selective barrier that provides defense against enteric pathogens. Mucus, essentially a hydrogel of highly glycosylated linear proteins, is densely packed with anti-microbial peptides such as defensins that can disrupt viral envelopes: another reason enteric viruses that transmit via oral-fecal routes are non-enveloped (Daher et al., 1986; Linden et al., 2008). The mucus layer also contains secretory antibodies that can neutralize virus before it reaches the tissue (Mantis et al., 2011). The outer mucus layer is constantly shed and passed down the digestive tract to be excreted. The epithelium itself forms a structural barrier to viral invasion including a dense brush border (microvilli) on the apical side and multiprotein adhesion complexes between neighboring epithelial cells (tight junctions) (Delorme-Axford and Coyne, 2011). Enteric viruses have adapted numerous strategies to invade through the mucosa. For example, adenovirus and poliovirus can both use tight junction proteins as entry receptors (Bergelson et al., 1997; Mendelsohn et al., 1989). However, most luminal bacteria and viruses never breach the mucosal barrier and therefore may not directly interact with immune cells (Kuss et al., 2008; Mantis et al., 2011).

Viral detection occurs through pattern recognition receptors, either intrinsically by an infected cell through recognition of cytosolic nucleic acids or extrinsically by recognition of endosomal nucleic acids (Figure 3). Cytosolic sensors are universally expressed across cell types to recognize DNA (cGAS) or RNA (RIG-I and MDA5), leading to downstream activation of adaptor proteins STING or MAVS, respectively (Andrejeva et al., 2004; Ishikawa and Barber, 2008; Yoneyama et al., 2004). Endosomal sensing is mediated primarily by toll-like receptors (TLRs) that are expressed by intestinal epithelial cells, DCs, and macrophages, recognizing double-stranded RNA (TLR3), single-stranded RNA (TLR7/8), and CpG motifs in double-stranded DNA (TLR9) and recruiting downstream adaptor and signaling proteins MyD88 and TRIF (Blasius and Beutler, 2010). TLR sensing is important as MyD88-deficient mice have increased susceptibility for multiple enteric viruses (Fejer et al., 2008; Hartman et al., 2007; McCartney et al., 2008; Thackray et al., 2012; Uchiyama et al., 2015).

Viral detection pathways lead to downstream activation of the transcription factor nuclear factor κB, which leads to production of pro-inflammatory cytokines including IL-1β, IL-6, IL-12, TNF-α, and IFNs (Kawai and Akira, 2011). IFNs are critical in antiviral immunity,

and mice lacking type I IFN receptor or the downstream adapter molecule STAT1 are highly susceptible to viral infections (Hwang et al., 1995; Ingle et al., 2018; Muller et al., 1994). Type I IFNs contribute to multi-pronged antiviral defense mechanisms that include promoting apoptosis of infected cells, antigen presentation pathways, and natural killer and cytotoxic T cell responses (Stetson and Medzhitov, 2006). While type I or II IFNs do not regulate viral load of chronic murine norovirus, these cytokines prevent the spread of virus from intestinal tuft cells to systemic extraintestinal sites such as lymph nodes and spleen (Baldridge et al., 2015; Nice et al., 2015). Most viruses have evolved mechanisms to evade the IFN response; for example, rotavirus targets IFN-regulatory factors (downstream of DNA/RNA sensors) to reduce the type I IFN response (Arnold and Patton, 2011). Type III interferon (IFNλ), which can be produced by epithelial and myeloid cells (Lauterbach et al., 2010), is also critical for control of enteric viruses in mice and induces long-lasting expression of IFN-stimulated genes relative to type I IFNs (Baldridge et al., 2017; Larsen et al., 2020; Ye et al., 2019). Consistently, mice lacking IFN-λ receptor exhibit high norovirus load in intestinal tissues and stool (Baldridge et al., 2017).

Nucleotide-binding oligomerization domain (NOD)-like receptors can be activated by enteric viruses though recognition of self-derived stress signals to induce the inflammasomes NLRP3 in immune cells or NLRP9 in IECs (Allen et al., 2009; Zhu et al., 2017). Inflammasomes are signaling complexes that activate caspase-1 or −11, resulting in inflammatory cell death, and secretion of the cytokines IL-1β and IL-18, which promote an adaptive antiviral response (Niu et al., 2019; Zhao and Zhao, 2020). The production of IL-18 and IL-22 by TLR5-stimulated DCs has been proposed to induce clearance of rotavirus (Zhang et al., 2014), while targeted deletion of NLRP9b in intestinal epithelial cells leads to diarrhea and increased rotavirus shedding in the feces (Zhu et al., 2017). The innate pathways described here enable broad detection of viruses that converge into a common pro-inflammatory response and conversely represent major targets for viral immune evasion strategies (Carty et al., 2021; Pichlmair and Reis e Sousa, 2007).

Innate responses occur rapidly, within hours of viral detection, and are critical for viral control during primary exposure. Additionally, innate cells contribute to induction of specific immunological memory through uptake and presentation of viral antigens to adaptive immune cells. Viral detection through pattern recognition receptors promotes antigen presentation through several mechanisms, including upregulation of costimulatory molecules, MHC class I and II, and CCR7-dependent migration to T cell zones in lymph nodes (van Montfoort et al., 2014). Antigen-presenting cells can also directly sample the intestinal lumen for antigens via trans-epithelial processes, though it is not known whether viruses can be sampled in this manner (Mazzini et al., 2014; Niess et al., 2005; Rescigno et al., 2001). Finally, specialized intestinal epithelial cells called M cells that overlay gut-associated lymphoid tissues such as Peyer’s patches can directly transport virus from the lumen through transcytosis, where they can be picked up for presentation (Dillon and Lo, 2019). However, several enteric viruses can also utilize M cells for entry and replication, and depletion of M cells in mice has been shown to limit infection with norovirus and reovirus (Dillon and Lo, 2019; Gonzalez-Hernandez et al., 2014). Initiation of adaptive immunity and formation of specific immune memory is key for protection against future infections.

INTESTINAL B CELLS AND IgA

B cells develop in the bone marrow, where they produce their B cell receptors by immunoglobulin gene rearrangements, which, following germinal center-mediated somatic hypermutation, provide virtually unlimited potential antigen recognition capacity. B cells are crucial players in mucosal immunity, especially as producers of secretory IgA, the most abundant antibody in mice and humans. Selective IgA deficiency in humans is associated with increased incidence of intestinal infections and more severe gastrointestinal symptoms, however, an estimated 85%–90% of IgA-deficient individuals are asymptomatic, suggesting alternate mechanisms such as increased IgM can compensate in absence of IgA (Yel, 2010). Following maturation of antigen-specific B cells at gut immune inductive sites, memory B cells and plasma cell precursors upregulate intestinal homing molecules α4β7 and CCR9 and migrate to the intestinal tissue (McNeal and Ward, 1995; Williams et al., 1998). Intestine-resident IgA plasma cells produce secretory dimeric IgA, which is transported to the lumen through the epithelial cells via polyIg-receptors (Mantis et al., 2011).

Secretory IgA is among the most important indicators of protection against enteric viral infection and can potentially neutralize virus in the mucus layer before it reaches host cells, preventing infection altogether. Indeed, clearance of enteric viruses has been positively correlated to the presence of specific intestinal IgA (Atmar et al., 2011; Blutt et al., 2012; Cheuvart et al., 2014; Lindesmith et al., 2003; Nishio et al., 1992; Ramani et al., 2015; Tacket et al., 2003; Unicomb et al., 1996). In contrast, circulating antibodies have limited access to the gut mucosa and hence are less capable of limiting the initial mucosal phase of enteric infections, though they have been shown to offer protection against the systemic phase of certain enteric pathogens (Faden et al., 1990; Hird and Grassly, 2012; Zeng et al., 2016). In many cases, serum-specific antibody titers correlate with protection against enteric viruses (Reeck et al., 2010; Velazquez et al., 2000), although it is unclear whether this is through direct control of infection or simply an indirect readout for control through secretory antibody induction. One study reported that 4 months after rotavirus infection, serum IgA levels could predict small intestine secretory IgA with 79% accuracy, whereas saliva (85%) and feces (92%) were more accurate predictors (Grimwood et al., 1988). Serum from adenovirus-infected mice has *in vitro* neutralizing activity but does not protect naive mice from enteric adenovirus infection, supporting the conclusion that serum antibodies cannot control mucosal infection (Lussier et al., 1987). Although an intestinal IgA response to SARS-CoV-2 has not been investigated, IgA antibodies dominate early specific antibody responses in the serum (monomeric, circulating), as well as in the saliva and lungs (secretory) (Sterlin et al., 2021). Furthermore, secretory IgA antibodies neutralize SARS-CoV-2 15-fold more effectively than their monomeric counterparts (Wang et al., 2021). Finally, mice lacking B cells fail to clear acute norovirus infection but are able to clear rotavirus infection, thus the absolute requirement for antibodies varies by virus (Chachu et al., 2008b; Franco and Greenberg, 1995; Karst et al., 2003). As most vaccines depend highly on humoral immunity, a better understanding of the role of circulating versus secretory antibodies as well as B cell-dependent and -independent pathways in the enteric anti-viral response is crucial.

Some evidence suggests that secretory antibodies generated by viral infections restricted to mucosal sites are short lived (<3 years) relative to serum antibodies generated by systemic infections (>10 years) (Slifka and Ahmed, 1996). Bacteria-specific intestinal IgA reportedly persists in monocolonized mice but declines rapidly in the presence of other microbiota, and additive increases in specific IgA were found after consecutive bacterial exposures, in contrast to prime-boost dynamics seen in peripheral antibody responses (Hapfelmeier et al., 2010). Mucosal IgA responses, therefore, may follow different dynamics than peripheral antibodies, and one possible mechanism for mucosal IgA degeneracy is continual replacement reflecting ongoing stimulation from the intestinal lumen. Rotavirus-specific IgA plasma cells can be detected in intestinal biopsies from the majority of human donors despite no recent history of rotavirus infection (Di Niro et al., 2010; Nair et al., 2016) and can be found in the lamina propria and bone marrow of mice 9 months after infection (Youngman et al., 2002). This suggests that despite potentially short-lived intestinal IgA, long-lived plasma cells may be able to quickly mount a humoral response upon re-infection. Studies on the longevity of intestinal humoral immunity are critical for understanding anti-viral mechanisms.

INTESTINE-RESIDENT T CELL RESPONSES

The majority of the immune cells found in the intestinal tissue are T cells, including peripherally recruited conventional TCRαβ T cells, which populate primarily the intestinal lamina propria, and tissue-resident innate-like T cells such as CD8αα TCRγδ, CD8αα, and CD4 CD8αα TCRαβ T cells primarily populating the intestinal epithelium (Cheroutre et al., 2011; Mayassi and Jabri, 2018). TCRαβ T cells primed in the gut-draining lymph nodes can migrate to the intestine where they functionally adapt, establishing permanent residency and memory characteristics (Bilate et al., 2020; Fonseca et al., 2020; Kiner et al., 2021; London et al., 2021).

Most mechanistic studies about the role of T cells in enteric virus infection derive from experiments in mice. While mice lacking both B and T cells become chronically infected with adenovirus or rotavirus (Dharakul et al., 1990; Franco and Greenberg, 1995; Umehara et al., 1984), animals lacking $CD8^+$ T cells show delayed clearance of these enteric viruses (Chachu et al., 2008a; Franco et al., 1997; Zhu et al., 2016), which suggests an important, but not essential, role for cytotoxic T cells. Along the same lines, adoptive transfer of norovirus-specific $CD8^+$ T cells can reduce the viral burden of $Rag^{-/-}$ mice persistently infected with norovirus (Tomov et al., 2013). Rotavirus-specific $CD8^+$ T cells have been found in Peyer's patches of infected mice expressing high levels of tissue homing receptors CCR9 and CXCR6 (Jiang et al., 2008). In humans, rotavirus-specific $CD8^+$ T cells were found in the peripheral blood and intestinal epithelium by tetramer staining; these cells also concomitantly express the gut-homing receptors CD103 and integrin β7 and produce IFN-γ (Newell et al., 2013; Wei et al., 2006, 2009). However, studies in animal models suggest that the production of IFN-γ or perforin and expression of bβ integrin by $CD8^+$ T cells are all dispensable for the control of rotavirus infection (Franco et al., 1997; Kuklin et al., 2000). On the other hand, perforin does have a role in protection against norovirus (Chachu et al., 2008a). The limited requirement for $CD8^+$ T cells may be due to partially redundant function with other cytotoxic immune cells such as innate lymphoid cells and

natural killer cells. For example, $CD8^+$ T cells detect virus-infected cells through viral peptide presentation on MHC-I, but several viruses evade $CD8^+$ T cell-mediated killing by downregulating MHC-I surface expression. In this case $CD8^+$ T cells are dispensable for viral clearance while natural killer cells can detect “missing self” and initiate cytotoxicity (Hansen et al., 2010; Koutsakos et al., 2019). In some cases, persistence of viral infection can be linked to evasion of $CD8^+$ T cell responses. For example, acute murine norovirus elicits effective $CD8^+$ T responses and can be cleared, while chronic murine norovirus recruits fewer and less functional $CD8^+$ T cells (Parsa et al., 2021; Tomov et al., 2013, 2017). While the mechanism of chronic murine norovirus evasion remains unclear, its selective infection of rare epithelial tuft cells may reduce antigen availability to $CD8^+$ T cells, while acute murine norovirus that infects myeloid cells may be more accessible. Additional studies are needed to define mechanisms of $CD8^+$ T cell-mediated viral control, how these pathways can be evaded by enteric viruses, and whether similar mechanisms apply during human infections.

Murine studies have also provided some understanding about the role of $CD4^+$ T cells in enteric viral clearance. $CD4^+$ T cell help is important for B cell class switching and affinity maturation, although some IgA is still found in $CD4^+$ T cell-deficient mice, indicating that IgA class switching can occur via both T cell-dependent and -independent pathways (Fagarasan et al., 2010; Hornquist et al., 1995; Snider et al., 1999). Accordingly, $CD4^+$ T cell-depleted mice show reduction in the generation of rotavirus-specific intestinal IgA, although they could still clear virus (Franco and Greenberg, 1997). Comparably, mice lacking $CD4^+$ T cells show higher norovirus load but eventually clear infection (Chachu et al., 2008a; Zhu et al., 2013, 2016). To gain more insights into the role of peripherally-recruited T cells in enteric viral infections, we fate-mapped naive T cells (Merkenschlager et al., 2021) in mice infected with several different enteric virus strains. We found that viruses that spread systemically, such as reovirus T1L (a virus in the same family as rotavirus) and acute norovirus CW3, preferentially recruit CD8 T cells to the intestine. In contrast, enteric adenovirus and chronic norovirus CR6, which do not spread systemically, induced the recruitment of activated $CD4^+$ T cells to the intestinal epithelium expressing CCR9, Ly-6A, granzyme B, and IFN-γ. Although mice infected with chronic norovirus did not clear infection, we found a role for norovirus-recruited $CD4^+$ T cells, but not reovirus-recruited $CD4^+$ T cells, in the clearance of heterologous adenovirus infection. Removal of TCR from $CD4^+$ T cells before adenovirus infection increased viral titers and delayed viral clearance, but removal of TCR post-infection did not impact viral clearance (Parsa et al., 2021). These findings suggest TCR-dependent differentiation but TCR-independent function of virus-recruited T cells, similar to what we previously proposed for other intestinal T cell subsets (Bilate et al., 2020). We also found that heterologous viral clearance by pre-existing virus-recruited $CD4^+$ T cells was dependent on IFN-γ secretion, which could be induced by stimulation with IL-12 and IL-18 without TCR engagement (Parsa et al., 2021). This suggests a unique differentiation pathway and TCR-independent function of virus-recruited intestinal $CD4^+$ T cells in cross-protective viral clearance.

In the epithelial layer, most T cells in mice and a large fraction in humans are TCR$\gamma\delta$ T cells (Guy-Grand et al., 1991). Murine studies demonstrated that TCR$\gamma\delta$ T cells actively monitor the intestinal epithelium and can quickly identify infected or stressed epithelial

cells (Hoytema van Konijnenburg et al., 2017). Upon activation, TCRγδ T cells exhibit cytotoxic properties and produce cytokines such as IFN-γ, TNF-α, and antimicrobial proteins (Cheroutre et al., 2011; Olivares-Villagomez and Van Kaer, 2018). Activated TCRγδ T cells can produce IFN-α and IFN-λ but were found to be dispensable for rotavirus clearance (Franco and Greenberg, 1997; Swamy et al., 2015). While part of these results could potentially be explained by redundancy in intestinal T cell subset function, the specific role of TCRγδ T cells in controlling enteric virus infections, particularly those with tropism for the epithelium, remains unclear but is an intriguing topic for further research.

HOST IMMUNITY, SUSCEPTIBILITY, AND HEALTH

Humans can suffer from multiple rotavirus, norovirus, and adenovirus infections throughout their lifespan, although the severity of disease is often reduced after repeated exposure (Gray et al., 2007; Velazquez, 2009; Velazquez et al., 1996). Epidemiological and clinical studies have demonstrated that strain-specific protective immunity can be generated after a single adenovirus, rotavirus, or norovirus infection, though there is conflicting evidence regarding the extent and duration of this protection (Gladstone et al., 2011; Simmons et al., 2013; Velazquez et al., 1996; Zhu et al., 2013). However, there are at least 30 serotypes of norovirus and 50 serotypes of adenovirus in circulation, with new variants constantly emerging, creating complications for long-term immunity (Lion, 2014; Ramani et al., 2014). Humans can be sequentially and even concurrently infected with different adenovirus strains within a span of 2 years (Gray et al., 2007). Host genetic diversity and environmental factors, including diet and gut microbiome, likely also contribute to variable outcomes in enteric virus susceptibility and immunity (Tan and Jiang, 2014).

The majority of deaths and severe illnesses from enteric viruses occur in children under 5 years old, and only neonatal mice are susceptible to symptomatic rotavirus or norovirus infection, whereas adult mice without pre-existing immunity are asymptomatic (GBD Diarrheal Disease Collaborators, 2018; Little and Shadduck, 1982; Sheridan et al., 1983) This suggests that age-related susceptibility to enteric viruses depends on both pre-existing immunity and maturation of the intestinal immune system. For example, lower levels of TLR3 are found in duodenal tissue from humans under 5 years old when compared to humans 6–20 years old, and, accordingly, TLR3 contributes to rotavirus control in adult mice but did not impact susceptibility in neonatal mice (Pott et al., 2012). Unfortunately, the short time frame in which mice can be symptomatically infected with rotavirus or norovirus creates difficulties in meaningful evaluation of protective immunity in murine models. Age-dependent aspects of mucosal immunity are an important consideration for timing of immunizations (discussed below).

While a balanced gut microbiota is known to protect against opportunistic bacterial infections, studies suggest that gut bacteria can both facilitate and protect against enteric virus infections under different circumstances. For example, antibiotic-treated mice have decreased susceptibility to poliovirus and rotavirus; findings possibly related to a microbiota-mediated suppression of the IFN-λ pathway (Baldridge et al., 2015; Kuss et al., 2011; Uchiyama et al., 2014). In contrast, another study reported that microbiota stimulates a homeostatic IFN-λ response (Van Winkle et al., 2022). Further, colonization

of segmented filamentous bacteria suppresses rotavirus infection in mice (Shi et al., 2019). In humans, gut microbiota composition has been correlated with susceptibility to rotavirus and norovirus (Rodriguez-Diaz et al., 2017), and the contrasting findings above suggest that different microbial species or compositions may either stimulate or suppress IFN-λ. Poliovirus binding of bacterial LPS was shown to enhance virion stability, suggesting a role for direct interactions between viruses and bacteria in addition to indirect stimulation of the immune system (Robinson et al., 2014). Preexisting viral infections may also impact viral susceptibility. For example, the presence of a specific strain of astrovirus in immunodeficient mice could protect against rotavirus and norovirus in an IFN-λ-dependent manner (Ingle et al., 2019). Together these findings suggest that diverse intestinal signals contribute to the overall state of IFN stimulation in the intestine, with consequences for susceptibility to viral infection.

Alongside commensal bacteria, the intestine is host to a diverse and abundant virome that is composed principally of bacteriophages and endogenous retroviruses (Neil and Cadwell, 2018). Intriguingly, while germ-free or antibiotic-treated mice have numerous intestinal abnormalities, including altered tissue morphology and reduced intestinal immune cells, norovirus infection was sufficient to reverse many of these phenotypes and protect against chemical tissue injury in a type-I-IFN-dependent manner, suggesting that in absence of a native microbiome or virome, typically pathogenic viruses can potentially promote intestinal homeostasis (Kernbauer et al., 2014). This emerging field of research has demonstrated that the concept of viruses as exclusively pathogenic is outdated, and that commensal viruses, like bacteria, may provide both benefits and detriments to the host (Neil and Cadwell, 2018).

Several studies have linked enteric viral infections to other intestinal diseases. Human norovirus infection and acute gastroenteritis have been associated with post-infectious irritable bowel syndrome and inflammatory bowel disease (Glass et al., 2009; Marshall et al., 2007). Chronic norovirus infection also triggers enhanced intestinal pathology in mice expressing a human Crohn disease susceptibility allele, suggesting that host gene-virus interactions can promote intestinal disease (Cadwell et al., 2010). Additionally, active infection with norovirus or HIV has been linked to changes in gut microbiota composition, suggesting that viral infection can lead to dysbiosis (Nelson et al., 2012; Vujkovic-Cvijin et al., 2013). Human studies have linked rotavirus and reovirus with Celiac disease, while enteric viral infections in mice were shown to impair the induction of regulatory T cells and promote inflammatory T cell responses to dietary antigen (Bouziat et al., 2017, 2018; Stene et al., 2006). These studies suggest that viral infections may disrupt homeostatic intestinal immune tolerance to microbiota and food in certain circumstances.

Finally, enteric viruses may impact health beyond the gut. A relationship between enteric infections and malnutrition, each increasing susceptibility to the other, has long been proposed (Scrimshaw et al., 1968; Tickell et al., 2020). Severe childhood diarrhea and malnutrition have in turn been correlated with stunted growth and increased risk of chronic adulthood conditions such as cardiovascular disease (Margolis, 2010; Schlaudecker et al., 2011). Rotavirus infection has also been implicated in increased risk of type I diabetes in humans and mice. One proposed mechanism is cross-reactivity between viral antigen and self-antigen leading to destruction of insulin-secreting cells, though only indirect evidence

for this exists (Burke et al., 2020; Gomez-Rial et al., 2020). A lot remains to be learned about mechanisms connecting enteric viruses and human diseases, but these observations highlight the importance of developing effective vaccines to prevent enteric virus infections.

TARGETING INTESTINAL IMMUNITY BY VACCINATION

Vaccines have been approved for each of the main enteric viruses discussed in this review except norovirus and overall have been highly successful at preventing serious viral disease. Poliovirus has been nearly eradicated from human populations after a global vaccination campaign (Razum et al., 2019), and mortality rate from diarrhea decreased 30% from 2010 to 2019, partly due to expanded distribution of rotavirus vaccines (De Jesus et al., 2020; IHME, 2019; Shah et al., 2017). However, enteric viruses still cause substantial mortality and health burden, especially for children in developing countries (GBD Diarrheal Disease Collaborators, 2018). Further, as viruses continuously evolve and adapt to evade immune responses and infect new niches, we must also adapt our immunization strategies. The COVID-19 pandemic has illustrated both the need for new vaccine strategies and relevance of mucosal immunity for prevention of infection.

Mucosal immune responses are highly compartmentalized such that the tissue of primary immunogen encounter is the site where the majority of effector and memory cells will traffic. The intestine-specific immune pathways of viral detection and response discussed above therefore depend on encountering the virus within the intestinal tract. Parenteral vaccines, for example those given in the intramuscular route, elicit strong peripheral immune responses but poor tissue immunity, and the circulating antibodies they generate have very limited access to mucosal tissue (Hird and Grassly, 2012; Holmgren and Czerkinsky, 2005; Zhaori et al., 1988). Further, several human studies have demonstrated that immunization at different mucosal sites (e.g. oral, rectal, nasal, vaginal) elicits mucosal antibody responses in the targeted tissue but produces variable antibody responses at other mucosal sites or even within different regions of the same mucosal tissue, thus, there is no universal route of mucosal immunization (Eriksson et al., 1998; Jertborn et al., 2001; Johansen et al., 2005; Johansson et al., 2004; Kozlowski et al., 1997; Ogier et al., 2005; Quiding-Jarbrink et al., 1997; van Splunter et al., 2018). The best route of immunization to generate intestinal immunity is therefore oral or rectal, although there is evidence that intranasal vaccination can elicit protective humoral and T cell responses in the intestine in some cases (Ciabattini et al., 2010; Esplugues et al., 2011; Ruane et al., 2013, 2016). Oral vaccines are particularly attractive as they are easy to administer without the need for sterile devices or trained personnel, a particular advantage in low-income countries where the need is highest. Thus, intestinal immunity generated through vaccination in the oral route is ideal for viruses that are restricted primarily to the gastrointestinal tract.

For viruses that infect through the fecal-oral route and then spread systemically (e.g. poliovirus, hepatitis A), parenteral and mucosal vaccines can both be effective. Intramuscular polio and hepatitis A vaccines produce circulating antibodies that prevent viral spread to the central nervous system or liver, respectively, protecting against serious disease. By contrast, the oral polio vaccine promotes both systemic and mucosal immunity,

including a robust IgA response that limits viral replication in the gastrointestinal tract (Nathanson, 2008; Wright et al., 2016) (Box 1).

For viruses that can infect multiple mucosal tissues including the intestine (e.g. adenovirus and HIV), ideal vaccines will promote broad immunity across mucosal and systemic sites, though this has proved evasive. Furthermore, there are some points of evidence that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect and replicate in the intestine, suggesting that induction of intestinal immunity may be an important consideration for vaccine design (Box 2). It has been suggested that oral vaccines can induce airway-homing memory B cells and nasopharyngeal IgA (van Splunter et al., 2018; Zhaori et al., 1988) and that nasal immunization can induce gut-homing B cells and intestinal immunity (Esplugues et al., 2011; Ruane et al., 2013, 2016). However, other studies have shown no intestinal immune response to nasal immunization (Ogier et al., 2005; Quiding-Jarbrink et al., 1997), suggesting that this cross-tissue protection may depend on immunization protocol. Oral immunization does not typically elicit protection in the genital tract (Eriksson et al., 1998; Kozlowski et al., 1997), providing a barrier to the development of oral vaccines for sexually transmitted pathogens. To protect multiple tissues, mucosal vaccines may require additional components to modulate immune cell trafficking. One option being investigated is the use of the vitamin A derivative retinoic acid (RA) to improve mucosal homing. RA has been shown to promote IgA class switching and to upregulate expression of CCR9 and integrin $\alpha 4\beta 7$ on T and B cells, leading to enhanced gut homing (Iwata et al., 2004; Lee et al., 2016; Mora et al., 2006; Ruane et al., 2016). Studies in mice have indicated that inclusion of RA with parenteral immunizations can promote gut, vaginal, and lung homing of T cells and increase specific intestinal IgA, resulting in improved protection against both bacterial and viral mucosal challenges (Hammerschmidt et al., 2011; Tan et al., 2011). In human trials, supplementation of oral typhoid vaccine with RA led to increased specific intestinal IgA and T cell expression of gut homing markers, though this effect was not seen with oral rotavirus, polio, or cholera vaccines (Lisulo et al., 2014; Mwanza-Lisulo et al., 2018). Defining further mechanisms of immune compartmentalization and cross-protection in mucosal tissue sites will be of great importance for improving mucosal vaccines.

Finally, immune compartmentalization exists even within the digestive tract, which may be an important consideration for vaccine design. We recently reported that immune responses in the proximal intestine are biased toward tolerance while the distal intestine is predisposed to more pro-inflammatory responses. As a consequence of this compartmentalization, immune tolerance to food proteins generated in the proximal intestine was not disrupted by pathogens infecting the distal intestine, but was disrupted by helminth infection restricted to the proximal intestine (Esterhazy et al., 2019). These findings suggest that targeting the distal intestine for vaccination might promote better protective immunity without the risk of disrupting homeostatic tolerance responses. For oral vaccines, the largest response is typically observed in the proximal intestine, though recent progress in vaccine delivery systems can enable a more targeted approach (Coffey et al., 2021; Johansson et al., 2004; van Splunter et al., 2018). Indeed, an adenovirus-vectored vaccine was found to be more immunogenic when delivered in radio-controlled capsules to the distal small intestine compared to the mid-small intestine (Kim et al., 2016).

ORAL VACCINES

There are four licensed oral vaccines for enteric viruses: two for rotavirus and two for poliovirus. Additionally, an oral vaccine for adenovirus is approved for military use. All approved oral vaccines use live attenuated or reassorted virus (Figure 1). Immunization with live virus works well in the oral route as they are naturally evolved to withstand degradation in the digestive tract and elicit immune responses through the same pathways as wild-type viruses, overriding intestinal immune tolerance. However, live strains come with a risk of genetic instability and can revert to virulence, as has been seen in rare cases (4.7 per 1 million) with the live polio vaccine (Platt et al., 2014) (Box 1). In more recent decades, the focus in viral vaccine development has shifted away from whole virus vaccines and toward compo-nent vaccines using viral protein (e.g. hepatitis B vaccine) or DNA/RNA (e.g. Pfizer/Moderna SARS-CoV-2 vaccines). These formulations are non-replicating and can be safer and more tar-geted than whole virus vaccines; however, they have so far been unsuccessful in the oral route due to poor survivability in the highly acidic and enzymatic environment of the digestive tract, the default state of immunological tolerance toward oral antigen, and a lack of safe and effective mucosal adjuvants (Lavelle and Ward, 2021). Viral vectors (e.g. AstaZeneca/Johnson and John-son SARS-CoV-2 vaccines) or virus-like particles (e.g. human papillomavirus vaccine) are more promising for oral use because their delivery and immunogenicity are similar to native strains, but they offer more opportunity for engineering and rational design. Importantly, vaccines using whole virus or viral vectors have native adjuvant properties and do not necessarily require additional adjuvant to stimulate mucosal immunity.

The immune response generated by existing oral vaccines using attenuated viral strains is overall similar to natural infection because the majority of immune stimulatory components remain intact. The inductive phase of oral rotavirus or poliovirus vaccination is characterized by a robust IgA response (Faden et al., 1990; Groome et al., 2017; Nishio et al., 1990; Ogra, 1995). In most studies, serum level of virus-specific IgA measured shortly after oral immunization is the best available correlate of vaccine protection (Angel et al., 2012; Cheuvart et al., 2014; Ogra, 1995; Plotkin, 2020). As discussed above, this is likely due to a correlation between circulating and secretory IgA, indicating that immunity from both natural infection and oral vaccination with enteric viruses depends on induction of secretory IgA, which can neutralize virus before it infects host cells and replicates.

T cell responses to oral immunization are less well studied than humoral responses, though T cells support mucosal IgA induction and very likely contribute to long-term protection. Of note, live vaccines are generally better at inducing T cell responses than component vaccines, which are often engineered and selected based on their ability to elicit humoral immunity (Gilbert, 2012). Following OPV, antigen-specific T cells in peripheral blood are characterized by expression of IFN-γ and gut-homing integrins (Vekemans et al., 2002; Wahid et al., 2005). T cell responses following rotavirus vaccination are poorly characterized, though low numbers of specific $CD4^+$ T cells expressing gut-homing integrins can be detected in peripheral blood 2 weeks after immunization (Parra et al., 2014).

The goal of oral vaccination is long-term protection against enteric infections, mediated by persistent mucosal antibodies as well as memory B and T cells that can be quickly activated upon infection to mount both local and systemic humoral and cellular responses. Polio-specific antibodies and T cells can be consistently detected in circulation decades after oral immunization, in line with the observation that OPV in childhood confers long lasting protection (Bianchi et al., 2021; Kelley et al., 1991; Sivak and Bobier, 1978; Wahid et al., 2005). Whether intestinal immunity from OPV is equally long-lasting has not been thoroughly assessed, though subjects that receive OPV in infancy show increased poliovirus-specific mucosal IgA after intramuscular boosting in adulthood (Herremans et al., 1999), possibly due to re-activation of long-lived memory cells. Longevity of rotavirus vaccine protection is less well characterized as vaccines have only been widely available in the last 15 years. Further, rotaviruses are still highly prevalent in human populations, unlike poliovirus, so detection of specific antibodies years after vaccination could be due to "boosting" by natural infection. However, because severe illness and mortality from enteric viruses primarily occurs in children under 5 years, decades-long vaccine protection may not always be required.

ADENOVIRAL VECTOR VACCINES

One strategy that has shown promise in recent years for mucosal vaccination is the use of adenoviral vectors, which display diverse tissue tropism depending on the subtype (Arnberg, 2009; Kang et al., 2020). An oral adenoviral vaccine used in the U.S. military that consists of live adenovirus-4 and −7 is well tolerated and generates long-lasting immunity against subsequent respiratory infection (Collins et al., 2020; Kuschner et al., 2013). This demonstrates that adenoviruses can generate immunity across mucosal tissues, including gastrointestinal and respiratory tracts. In addition, adenoviruses offer great potential as flexible vaccine delivery systems because strains with different characteristics can be selected or engineered to target appropriate immunity for a given pathogen, as was recently reviewed (Barry et al., 2020). Other practical advantages of adenoviral vectors are that they do not integrate into the host genome, making them relatively safe, and they can be stably stored at room temperature, making them easy to distribute.

Oral vaccines using adenoviral vectors are under investigation for several viruses. One notable oral platform is VXA, which is currently in clinical trial for vaccination against influenza, norovirus, and SARS-CoV-2 (Vaxart, USA). VXA is a replication-defective adenovirus-5 vector expressing a TLR3 adjuvant (Liebowitz et al., 2020; Scallan et al., 2013). Phase 1 and 2 clinical trials with VXA expressing influenza or norovirus proteins have indicated induction of mucosal IgA as well as a robust mucosal homing $CD4^+$ and $CD8^+$ T cell response. By contrast, reports on whether parenteral adenoviral vaccines such as VXA can elicit mucosal antibody responses have been mixed (DOI 10.1101/2021.08.22.21262168) (Declercq et al., 2022). Pre-clinical studies showed that oral immunization with VXA encoding SARS-CoV-2 spike protein (VXA-Cov2) protected hamsters against severe disease (Johnson et al., 2022). Phase 1 clinical tri-als with VXA-Cov2 found induction of specific IgA in saliva and nasal fluid (Johnson et al., 2022). These early reports provide promising evidence that oral vaccination using adenoviral vec-tors can generate mucosal immune responses in both the gastrointestinal tract and airway, and

a room-temperature-sta-ble oral tablet formulation would certainly be valuable for widespread COVID-19 vaccine distribution. However, the efficacy of these vaccines remains unproven in humans and is not yet be-ing tested in developing countries.

GLOBAL EFFICACY OF ORAL VACCINES

Enteric viruses are ubiquitous across the globe, contributing to health burden in both low- and high-income countries. However, out of 1.6 million deaths from diarrhea in 2016, nearly 1.5 million occurred in south Asia and sub-Saharan Africa, while only 30,000 occurred in high-income countries (GBD Diarrheal Disease Collaborators, 2018). Unfortunately, there is growing evidence that oral vaccines are less effective in low-income settings. Oral rotavirus vaccines report 85%–100% efficacy at preventing severe disease in middle- and high-income countries, but only 40%–60% in low-income countries (Armah et al., 2010; Jiang et al., 2010; Madhi et al., 2010; O'Ryan and Linhares, 2009; Ruiz-Palacios et al., 2006; Vesikari et al., 2006, 2007; Zaman et al., 2010). 3 doses of OPV resulted in nearly 100% seroconversion of children in the USA but only 70%–90% seroconversion of children in India (John, 1976; McBean et al., 1988). Similar discrepancies have been described for oral vaccines against *Vibrio cholera* and enterotoxigenic *E. coli* (Hallander et al., 2002; Svennerholm et al., 2021), indicating that the problem is not confined to anti-viral immunity.

A number of correlates have been proposed to explain vaccine failures in low-income settings, though methods and results in these studies are highly variable, making it difficult to draw firm conclusions (Parker et al., 2018). Additionally, many factors that impact gut immunity (e.g. host genetics, infection history, diet, microbiota) have complex relationships with each other, making it difficult to pinpoint specific causative factors on a population scale. For example, diet and microbiota play substantial roles in shaping the intestinal immune system, vary highly across socioeconomic regions, and are linked to infection susceptibility and gut homeostasis. Additionally, concomitant infection with enteric pathogens in vaccinated individuals could impact the initiation of immune responses to oral vaccines in gut-draining lymph nodes. However, observational studies have not identified consistent links between nutrition or commensal microbiota composition and oral vaccine efficacy, possibly because of the complex nature of the variables involved (Parker et al., 2018; Savy et al., 2009), highlighting the need for comprehensive longitudinal studies.

Enteric infection and vaccination history of both children and their mothers have been linked to oral vaccine efficacy. Infants from low-income countries are more likely to have rotavirus-specific serum IgA prior to immunization than infants from high-income countries (Cunliffe et al., 2014). Presence of specific maternal antibodies has been negatively associated with oral vaccine immunogenicity, though there is conflicting evidence regarding a relationship to breastfeeding, likely due to the complex nature of maternal-derived immune factors in breastmilk (Becker-Dreps et al., 2015; Moon et al., 2016; Rennels, 1996; Rongsen-Chandola et al., 2014; Sabin et al., 1963). Intriguingly, maternal helminth infection in the third trimester correlated with increased IgA responses to oral rotavirus or poliovirus vaccine (Clark et al., 2016).

Several studies suggest that certain concomitant enteric immune responses may interfere with vaccination. Diarrhea concurrent with OPV reduces seroconversion, suggesting that either specific conflicting immune responses or general intestinal inflammation and dysfunction can disrupt oral immunization (Parker et al., 2014). Immunogenicity of oral rotavirus or poliovirus vaccines was reduced by concurrent infection with nonpolio enterovirus, although several detected enteric pathogens did not significantly impact oral immunization (Taniuchi et al., 2016). Further, giving oral rotavirus and poliovirus vaccines on the same day lowers rotavirus seroconversion but not poliovirus seroconversion (Emperador et al., 2016). Finally, intestinal IgA responses to OPV wane with age and are sometimes undetectable in adults, even if there is pre-existing circulating immunity due to prior intramuscular vaccination during infancy (Brickley et al., 2019). These findings demonstrate that immune responses in the intestine may interfere with each other, though it may depend on certain shared pathways. Detangling specific mechanisms of disruption will be critical for finding solutions. The majority of studies above have assessed factors related to failure in seroconversion after oral vaccination. However, IgA seroconversion itself is less predictive of oral vaccine protection in low-income countries, suggesting that even when an initial immune response is mounted there are more complex environmental factors governing long-term mucosal immunity (Angel et al., 2012). To our knowledge studies have not yet addressed environmental factors in longevity of mucosal antibody responses.

Altogether, it is unlikely that a single factor is responsible for vaccine failure in developing countries. Chronic enteric infections, diarrhea, and malnutrition lead to a cluster of related downstream effects including gut barrier dysfunction, dysbiosis, increased inflammatory stimulation, and immune dysregulation. One explanation for vaccine failure is that a state of bystander hyperactivation of the intestinal immune system, potentially in conjunction with pre-existing antibodies, leads to clearance of live attenuated oral vaccines before a specific mucosal response can be generated. Such mechanism might then be insufficient to clear non-attenuated virus, leading to illness. Another possible explanation is that conflict with other ongoing immune responses in the intestine leads to poor responsiveness even if the vaccine is delivered to immune inductive sites. There may be a critical window for oral immunization between the time that maternal antibodies wane and other conflicting intestinal immune responses accumulate. Variation in prevalent circulating viral serotypes across geographical regions is also an important consideration in vaccine design. Understanding the basis for oral vaccine failure will be critical for design of new strategies, and these studies also demonstrate the importance of testing oral vaccines in a variety of geographical and socioeconomic settings because gut immunity is highly impacted by environment. Finally, they show that although vaccines are critical in the fight against global disease there will be no silver bullet for enteric viruses in low-income settings without basic access to food, clean water, and medicine.

CONCLUDING REMARKS

Enteric viruses are a major cause of mortality and global health burden, though the relatively low impact of these viruses in high-income countries shows that many of these deaths could be prevented with access to existing medical interventions. Nevertheless, as new viruses will continually emerge, it is important to continue efforts to understand viral pathogenesis and

immunity, especially at mucosal sites where the majority of viral infections begin. Human studies in this field are challenging, but much needed insight could be gained from directly studying intestinal immune responses to viral infection and vaccination through biopsies and sampling of fecal antibodies. The majority of our mechanistic understanding of intestinal immunity comes from mouse studies; however, lab mice fail to capture the complexity of the human intestinal immune landscape as they typically lack an infection history and have a stable diet and environmental niche. Use of pet shop or “wildling” mice will likely provide more accurate models for understanding intestinal immunity. Better understanding of human intestinal anti-viral immunity can be combined with advances in vaccine technology to target effective and long-lasting protection in a variety of environmental contexts. We see great promise in oral vaccination for existing and emerging viruses if this can be achieved.

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Box 1.

Oral polio vaccines: A success story and a cautionary tale

The polio vaccination campaign has overall been highly successful, resulting in near-global eradication of polio. Oral polio vaccination (OPV) promotes both mucosal and systemic immunity, including a robust IgA response that limits viral replication in the gastrointestinal tract (Nathanson, 2008; Wright et al., 2016). Intramuscular inactivated polio vaccines (IPVs), by contrast, do not promote a mucosal immune response but do produce circulating antibodies that prevent viral spread to the central nervous system and subsequent paralysis (Hird and Grassly, 2012). Both vaccines are highly effective and promote long-lasting protection, but parenteral vaccination does not prevent viral replication or subsequent community transmission due to the lack of mucosal immunity (Herremans et al., 1999; Shulman et al., 2015). Further, the OPV is both cheaper and easier to administer (Zimmermann et al., 2020). The main drawback of OPV is that in rare cases (4.7 per 1 million) the live attenuated virus can revert to neurovirulence, causing paralysis, whereas IPVs use inactivated virus and are not associated with the same risk (Platt et al., 2014). For this reason, most high-income countries have transitioned to IPV (Bandyopadhyay et al., 2015). Vaccine schedules giving first IPV then OPV have been shown to promote mucosal immunity while limiting potential risks, because systemic immunity is already in place upon exposure to the live vaccine (Alexander et al., 2004; Domok, 1984; Modlin et al., 1997). This indicates that combination parenteral and mucosal vaccination may be an option for combatting viruses, particularly those where immunity in multiple tissue sites is needed. However, formulation of effective oral vaccines without live virus remains a critical next step for vaccine development.

Box 2.

Evidence for intestinal SARS-CoV-2 infection

SARS-CoV-2, the virus behind the COVID-19 pandemic, which killed more than 3 million people in 2020 alone (Simonsen and Viboud, 2021), is thought to primarily spread through respiratory droplets and replicate in airway epithelial cells (Stadnytskyi et al., 2020). There is some evidence for SARS-CoV-2 infection in the gastrointestinal tract, though the origins of such infections are unclear. Fecal-oral transmission has been proposed (Guo et al., 2021), though unlike other known human enteric viruses, SARS-CoV-2 has an envelope and therefore likely does not survive well in the stomach. It is also possible that SARS-CoV-2 can disseminate to the gut from the respiratory tract via circulation. SARS-CoV-2 enters cells using primarily ACE2, which is highly expressed on intestinal epithelial cells (Hamming et al., 2004; Hoffmann et al., 2020; Hu et al., 2021), and SARS-CoV-2 can infect and replicate in human intestinal organoids and organ chips (Bein et al., 2021; Lamers et al., 2020). While SARS-CoV-2 RNA is readily found in stool samples of infected individuals, detection of live, replicative virus has been difficult, perhaps due to viral isolation methods or timing of sample isolation (Holshue et al., 2020; Pedersen et al., 2022; Wolfel et al., 2020). We did not find any clinical symptoms or immune activation in the intestine or lungs of mice orally infected with ten times the lethal intranasal dose of mouse-adapted SARS-CoV-2 (unpublished data). However, it should be noted that this virus was adapted for intranasal infection, which could affect the intestinal tropism of the virus (Leist et al., 2020). Nevertheless, intragastric inoculation of SARS-CoV-2 in non-human primates manifested in productive infection of both respiratory and intestinal tissue (Jiao et al., 2021). Interestingly, SARS-CoV-2 shedding in stool can persist even after respiratory symptoms subside (Wu et al., 2020). Additionally, one study detected SARS-CoV-2 N protein in intestinal enterocytes in 5 of 14 individuals an average of 4 months after COVID-19 diagnosis, indicating prolonged viral shedding of SARS-CoV-2 (Gaebler et al., 2021). Finally, some patients infected with SARS-CoV-2 also display acute gastrointestinal symptoms (Pan et al., 2020; Wang et al., 2020). However, direct evidence of gastrointestinal damage caused by SARS-CoV-2 is lacking and needs further investigation.

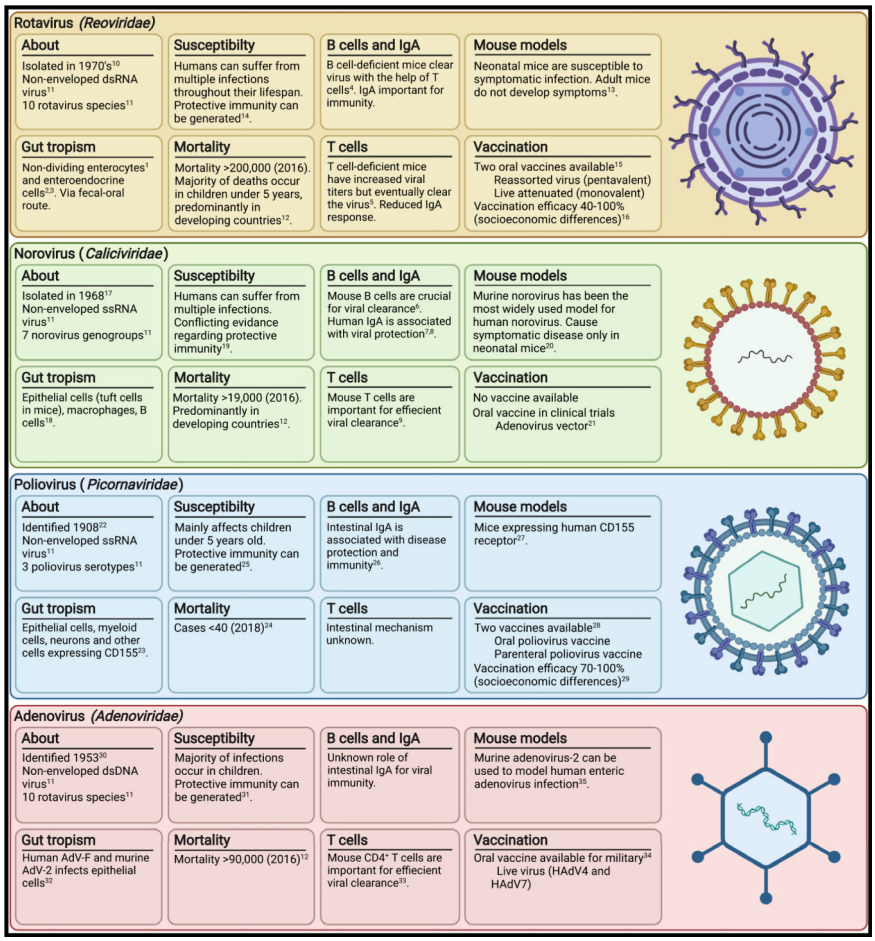

Figure 1. Pathogenic enteric viruses

Key features of enteric viruses, natural immunity, and vaccines.

References: [1](Lundgren and Svensson, 2001); [2](Hagbom et al., 2011); [3](Saxena et al., 2016); [4](Franco and Greenberg, 1995); [5](Franco and Greenberg, 1997); [6](Chachu et al., 2008b); [7](Lindesmith et al., 2003); [8](Ramani et al., 2015); [9](Chachu et al., 2008a); [10](Bishop et al., 1973; Flewett et al., 1973); [11](Howley et al., 2020); [12](GBD Diarrheal Disease Collaborators, 2018); [13](Little and Shadduck, 1982; Sheridan et al., 1983); [14](Bhandari et al., 2014; Ruiz-Palacios et al., 2006; Velazquez et al., 1996); [15](Burnett et al., 2020); [16](Armah et al., 2010; Jiang et al., 2010; Madhi et al., 2010; O'Ryan and Linhares, 2009; Ruiz-Palacios et al., 2006; Vesikari et al., 2006, 2007; Zaman et al., 2010); [17](Kapikian et al., 1972); [18](Baldridge et al., 2016; Elftman et al., 2013; Gonzalez-Hernandez et al., 2013, 2014; Grau et al., 2017; Karst and Wobus, 2015); [19](Newman and Leon, 2015); [20](Roth et al., 2020); [21](Kim et al., 2018); [22](Eggers, 1999); [23](Mendelsohn et al., 1989; Nomoto, 2007); [24](Chard et al., 2020); [25](Nathanson, 2008); [26](Wright et al., 2016); [27](Khan et al., 2014; Koike et al., 1991); [28](Connor et al., 2022); [29](John, 1976; McBean et al., 1988); [30](Hilleman and Werner, 1954; Rowe et al., 1953); [31](Lion, 2014); [32](Greber and Flatt, 2019; Hashimoto et al., 1966); [33](Parsa et al., 2021); [34](Collins et al., 2020; Kuschner et al., 2013); [35](Hashimoto et al., 1966).

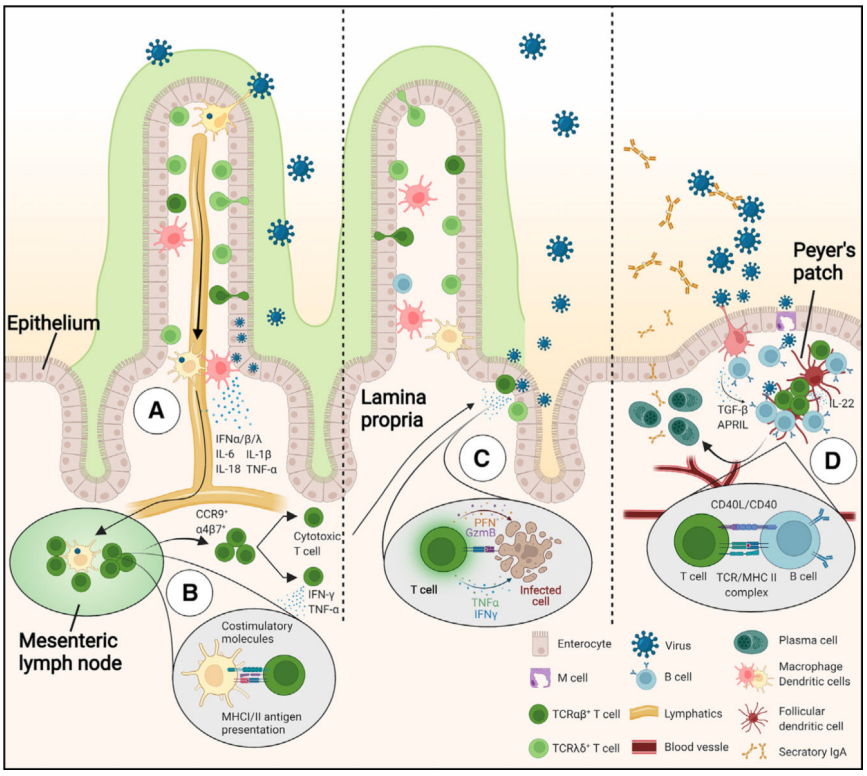

Figure 2. Intestinal immunity during viral infections

(A) Early recognition of viruses via pattern recognition receptors such as intracellular DNA and RNA sensors by innate immune cells results in an interferon and cytokine response. Virus and viral antigen uptake by dendritic cells, macrophages, and epithelial M cells leads to activation of the adaptive immune system.

(B) Dendritic cells in the lamina propria migrate to the draining mesenteric lymph nodes and present viral antigens to virus-specific T cells.

(C) Activated T cells migrate to the intestinal tissue and elicit antiviral immunity by cytokine secretion or cytotoxic activity.

(D) B cells activated in Peyer’s patches undergo IgA class switching and differentiate into plasma cells with the help of follicular T helper cells. Intestinal plasma cells produce secretory IgA that can neutralize viruses in the mucosa.

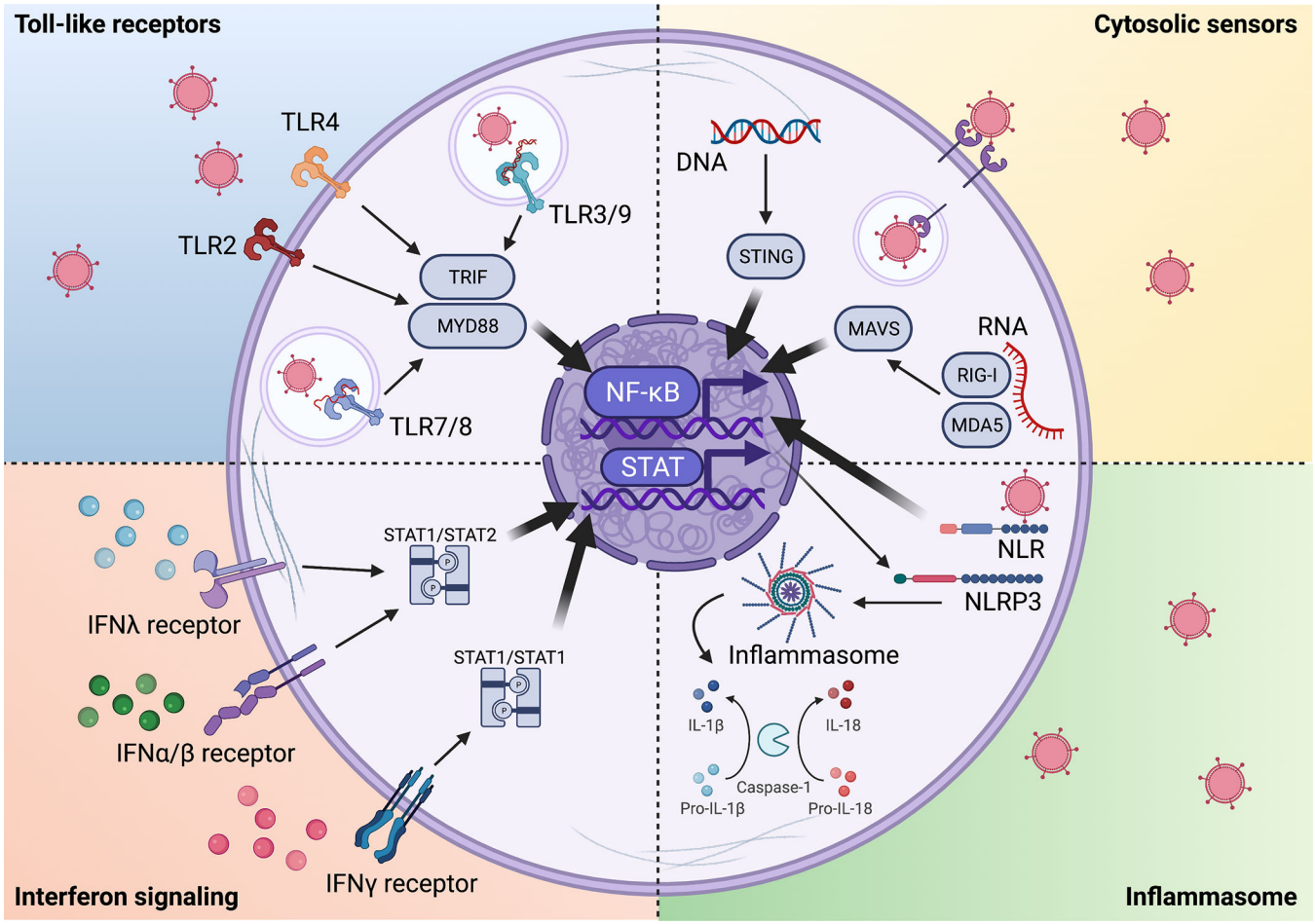

Figure 3. Detection of viruses by pattern recognition receptors

Virus-derived RNA and DNA can be recognized by toll-like receptors (TLRs) and cytosolic sensors, resulting in the secretion of pro-inflammatory cytokines and IFNs. Inflammasome activation results in cytokine maturation and secretion and inflammation-induced cell death. IFNs activate gene expression programs that are important for downstream anti-viral immunity.