

OPINION

# A Working Model of How Noroviruses Infect the Intestine

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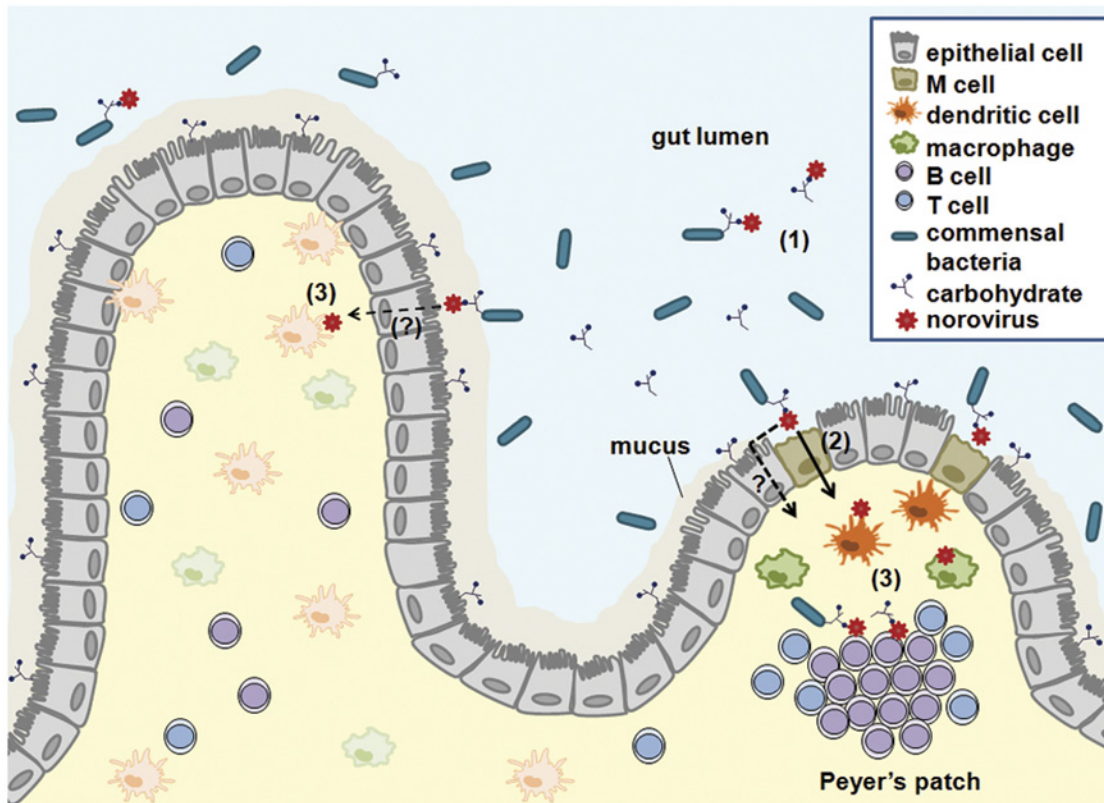
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## Introduction

Human noroviruses (HuNoVs) cause a majority of gastroenteritis outbreaks across the globe and are the leading cause of severe childhood diarrhea and foodborne disease outbreaks in the United States [1,2]. In impoverished countries, they are estimated to cause over one million clinic visits and 200,000 deaths in young children annually [3]. However, the mechanisms used by noroviruses (NoVs) to infect the intestinal tract and cause disease are not well understood, primarily due to the paucity of cell culture and animal model systems. Recent major advances in developing such models now leave the field poised to tackle these critical questions. The goal of this opinion article is to propose a working model of early steps involved in intestinal infection by NoVs. In this model, NoVs bind carbohydrates on the surface of specific members of the intestinal microbiota and/or enterocytes and are then transcytosed across the intestinal epithelial barrier to gain access to their target immune cells. Evidence supporting each step of this model will be discussed. We also include a brief discussion of how NoVs cause disease as it relates to our model.

## NoVs Are Transcytosed Across Enterocytes in the Absence of Viral Replication

HuNoV and murine NoVs (MuNoV) are transcytosed across intestinal epithelial cells in vitro [4,5], although they have not been shown to productively infect these cells in immunocompetent hosts (reviewed in [6]). Transcytosis of MuNoV across polarized murine intestinal epithelial cell monolayers does not disrupt tight junctions, is enhanced by B cell coculture, and is mediated by cells with characteristics of microfold (M) cells [4], a specialized cell type within the intestine responsible for sampling particulate antigen [7]. In a similar system, HuNoV virus-like particles were visualized on the basolateral side of cell nuclei from polarized Caco-2 cells [5], suggesting transport of particles through epithelial cells. However, whether particles were released from cells, whether particle transport modulated tight junction integrity, or whether a specialized cell type such as M cells mediated this process was not investigated. The importance of M cells for the efficient initiation of MuNoV infection in vivo was subsequently demonstrated by infecting mice depleted of M cells and observing reductions in viral titers in the intestine [8]. Furthermore, this partial, in contrast to complete, reduction of MuNoV infection in M cell-depleted mice suggests the presence of additional viral uptake routes across the intestinal barrier. Reovirus, a double-stranded RNA virus that infects enterocytes, similarly requires M cells for efficient infection [8], and other enteric pathogens also exploit M cells to



**Fig 1. A working model for NoV intestinal infection.** Multiple studies demonstrate that NoVs bind carbohydrates. These carbohydrates are expressed on enterocytes and secreted into the gut lumen. Furthermore, enteric bacteria can express similar carbohydrates. NoVs may bind to such carbohydrates in any of these contexts (1). NoVs are then transcytosed across the intestinal epithelium via M cells (2) and additional as-yet-to-be-identified pathways. Following transcytosis, NoVs infect dendritic cells, macrophages, and B cells (3). Depending on the species, infection can occur in the presence or absence of carbohydrates. Free carbohydrates or bacterially expressed carbohydrates may be cotranscytosed with the virus. Immune cell infection and putative concomitant viral-bacterial antigen presentation during NoV infections could have significant consequences on the nature and magnitude of antiviral immune responses.

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infect the host [9]. Hence, we speculate that similar mechanisms are used by HuNoV to cross the intestinal epithelial barrier (Fig 1).

### NoVs Infect Innate Immune Cells

Upon crossing the epithelial barrier, viral particles next encounter immune cells in the lamina propria and lymphoid follicles, including Peyer's patches (Fig 1). The evidence that NoVs infect immune cells is numerous, although intestinal epithelial cells are also infected in case of bovine NoV [10]. MuNoV lytically replicates in antigen-presenting dendritic cells and macrophages in vitro [11]. In vivo, MuNoV antigen is detectable in cells morphologically resembling dendritic cells and macrophages and in cells positive for the macrophage marker F4/80 [11,12]. Although one report failed to observe HuNoV replication in peripheral blood-derived macrophages and dendritic cells in vitro [13], HuNoV appears to target intestinal immune cells in vivo consistent with the tropism of MuNoV: viral antigen was detected in intestinal lamina propria cells from a biopsy sample of a HuNoV-infected person [13]; and inactivated HuNoV particles bind to lamina propria cells in human intestinal tissue sections [14]. Additional support comes from animal models of HuNoV infection: chimpanzees and immunodeficient mice infected with a HuNoV contain viral antigens in cells resembling, or confirmed to be,

dendritic cells or macrophages [15,16]. Finally, monkeys infected with genetically related reoviruses and bovine NoV also contain virus antigen-positive intestinal lamina propria cells [10,17]. While detection of viral intermediates in antigen-presenting cells *in vivo* may be due to phagocytosis of apoptotic epithelial cells infected by bovine NoV, viral antigen was not detected in enterocytes in any of the other examples. This, along with the ability of MuNoV to infect innate immune cells *in vitro*, supports that these cell types are bona fide NoV targets. It is likely that infection of antigen-presenting cells influences the immune outcome to infection, which was recently demonstrated for MuNoV [18].

## NoVs Infect Adaptive Immune Cells

In addition to macrophages and dendritic cells, B cells were recently identified as targets of NoV infection [19]. Both HuNoV and MuNoV productively infect B cell lines *in vitro*, establishing the first cell culture system for HuNoV. B cell infection appears to be distinct from macrophage or dendritic cell infection in that no cytopathic effect is observed in infected cultures and is distinct from lytic infection of intestinal B cells by rotavirus [20]. Whether this is due to true noncytopathic B cell infection (precedence exists for noncytopathic infection by a nonenveloped, positive-sense RNA virus [21]) or the low infectivity of this cell type remains to be determined. B cells are also target cells *in vivo*: MuNoV titers are reduced in mice lacking B cells, and MuNoV antigen is detected in B cell zones of Peyer's patches of infected interferon- and interleukin-10-deficient mice [22,23]. MuNoV genome and nonstructural protein are detected in Peyer's patch B cells of infected mice [19]; and HuNoV-infected chimpanzees contain virus antigen-positive B cells in the small intestine [16]. Given that several MuNoV strains can persistently infect mature B cells *in vitro* [19], we speculate that B cells may also provide a reservoir for persistent MuNoV infections *in vivo*.

## Enteric Bacteria Serve as a Co-Factor for NoV Infection

Enteric bacteria can enhance viral infections [24] since poliovirus, reovirus, and mouse mammary tumor virus infections are reduced in antibiotic-treated or germ-free mice [25,26]. Similarly, antibiotic treatment of mice resulted in a significant reduction in MuNoV yield in the intestine when compared to untreated mice [19]. Thus, commensal bacteria can stimulate NoV infections *in vivo* and may influence the immune response to viral infection. Although enteric bacteria are not required for MuNoV infection *in vitro* [11], they significantly enhance HuNoV infection of B cells *in vitro* [19].

The mechanism(s) of bacterial enhancement of enteric virus infection is not well understood. While binding to bacterial lipopolysaccharide (LPS) is one mechanism [26,27], LPS does not enhance HuNoV infection of B cells *in vitro* [19]. Instead, histo-blood group antigen (HBGA)-expressing bacteria and free HBGA stimulate HuNoV infection of B cells, while non-HBGA-expressing bacteria do not [19]. HBGAs are neutral carbohydrates found on proteins or lipids that are bound by individual HuNoV strains and their expression correlates with a person's susceptibility to infection (reviewed e.g., in [28]). Virus binding to HBGAs expressed on host enterocytes has been thought to facilitate retention in the intestine and to counter the movement of particles via peristalsis. However, expression of appropriate HBGAs on enterocytes in culture does not mediate infection [29]. Interestingly, certain pathogenic and commensal enteric bacteria also express carbohydrates indistinguishable from human HBGAs [30–34], and HuNoV particles bind to HBGA-expressing bacteria [35]. Interaction of HuNoV with free or bacteria-bound HBGAs enhances attachment to, and infection of, B cells [19]. While an interaction between specific bacteria and MuNoV has not been shown to date, MuNoV binds carbohydrates such as sialic acids [36] which are abundant on the surface of enteric bacteria

[37]. Thus, we speculate that NoVs bind specific carbohydrates on the surface of certain bacteria instead of, or in addition to, enterocytes to enhance infection of the host (Fig 1).

Bacteria may also play additional roles *in vivo* by enhancing the transcytosis of NoVs across the intestinal epithelium. While HuNoV and MuNoV can be transcytosed across polarized cells in the absence of bacteria *in vitro* [4,5], there are additional physical barriers (e.g., a thick mucus lining) impeding their access to the epithelium in the complex environment of the intestinal lumen. To overcome such physical barriers, we hypothesize that NoVs may bind to motile bacteria that can traverse the mucus layer [38]. In addition, the host continuously samples its luminal cargo; for example, commensal bacteria in complex with secretory immunoglobulin A (sIgA) are taken up via Peyer's patch-associated M cells and delivered to underlying dendritic cells and macrophages [39]. Viral particles bound to bacteria could thus be delivered to permissive immune cells. Since sIgA complexes are generally anti-inflammatory [40], this might account for the mild inflammation observed during MuNoV infection [23]. Conversely, it is possible that NoVs actively drive transcytosis of commensal bacteria. Studies that provide mechanistic insights into the bacterial enhancement of NoV infection are clearly needed and promise to provide important insights into the interplay between the intestinal microbiota, enteric viruses, and the host.

## Gaps in Understanding NoV Pathogenesis

In this section, we briefly speculate how the proposed model might relate to unanswered questions in NoV pathogenesis. Given the length restrictions, we limit our discussion to i) viral shedding and ii) mechanisms of gastroenteritis.

First, the source of virus shed in the feces is one conundrum that exists in NoV pathogenesis. Shedding varies greatly with peak titers ranging between  $10^5$ – $10^9$  genome copies/g of feces and lasting days to months [41], and high viral titers likely contribute to the explosive nature of NoV outbreaks. However, this high-level shedding appears inconsistent with the low-level viral replication in cultured B cells [19]. A likely explanation for this discrepancy is that B cell lines do not entirely mirror the properties of intestinal B cells *in vivo*. Additionally, intestinal macrophages and dendritic cells could support high levels of NoV replication similar to MuNoV infection [11]. Finally, it should be noted that only sections of small intestines have been analyzed for HuNoV antigens thus far. It is possible that a population of highly permissive cells in other regions of the intestine (e.g., cecum or colon) or an unrecognized virus reservoir at an extraintestinal site (e.g., liver with shedding into bile fluids) is responsible for the robust viral shedding.

Second, one question raised by our model is how NoVs cause gastroenteritis in the absence of enterocyte infection. We propose that one or more of the following mechanisms may be at play: (1) Infection of immune cells could trigger the release of pathologic levels of proinflammatory cytokines, although NoV infections are only modestly inflammatory based on available data [6]. (2) NoVs could encode a viral enterotoxin similar to the rotavirus NSP4 protein [42], and secretion of this enterotoxin from infected immune cells could act on enterocytes basally to cause epithelium dysfunction. (3) NoVs could stimulate the transcytosis of commensal bacteria that are generally considered nonpathogenic because they cannot breach the intestinal epithelium. In this scenario, pathologic mechanisms encoded by the bacteria would contribute to NoV-associated disease. (4) NoV infection of intestinal macrophages could cause functional changes that result in altered motor function, since intestinal macrophages closely interact with the enteric nervous system and regulate gut motility [43–45]. This crosstalk between macrophages and neurons is also regulated by the microbiota [43]. To explore these scenarios, studies in NoV animal models displaying disease symptoms and, particularly in case of the latter two, including a functional microbiota, are needed in the future.

## Concluding Remarks

The NoV field has made great strides in recent years elucidating the cell tropism and mechanisms of intestinal infection, although these areas remain incompletely defined and sometimes controversial. Herein, we have evaluated and integrated available data often from *in vitro* and mouse studies to propose a working model of intestinal infection for NoVs: in this model, we propose that NoVs bind to bacterial and/or host carbohydrates within the gut lumen, transcytose across the intestinal epithelium, and are delivered to target immune cells in the lamina propria. We further speculate that cotranscytosed carbohydrate (free or as part of bacteria) can directly stimulate NoV attachment to, and infection of, these target cells. Future studies are needed to determine whether NoV infections in all host species (e.g., humans, mice, dogs, and pigs) follow a similar pattern such as the one proposed herein or vary significantly in their infection route(s).

Collectively, it is our hope that by sharing this model we will facilitate experimental approaches to test individual aspects of the model and that such studies will advance our understanding of NoVs and enteric viruses in general.

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**Note added in proof:** This article was written prior to publication of two manuscripts elucidating the interaction of MNV with its host and the microbiota by Kernbauer et al. [46] and Baldrige et al. [47], thus, does not incorporate this new information.

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