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# Basic Virology: Human Norovirus Protein Immunity

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## Introduction

Noroviruses (NVs) cause most outbreaks of acute gastroenteritis and account for 267 million infections and more than 200,000 deaths each year.1 Strains belonging to genotype GII.4 have led to 6 pandemics since 1995 and pose a major health and economic burden. Numerous challenges have hampered the study of NVs and the development of an effective vaccine. Such challenges include the inability to propagate NVs in established cell lines; the rapid emergence of novel GII.4 strains that escape herd immunity; and the complexity of host exposure histories and determinants of susceptibility, which complicate the interpretation of immunologic studies. Consequently, key questions, such as what constitutes an effective and durable NV immune response, remain unanswered [1].

In this issue of Cellular and Molecular Gastroenterology and Hepatology, Lindesmith a particularly important and understudied area of human NV research: the cellular immune response following acute infection. Most studies to date have focused on humoral immunity and have shown that antibodies that block NV attachment to host histoblood group antigens (HBGAs) are associated with protection from reinfection [2]. However, such antibodies are highly strain-specific and may be short-lived; moreover, a robust antibody response is not always sufficient or necessary for protection against NV, suggesting that additional immune mechanisms may be at play. Indeed, innate immunity and T cells are critical during mouse NV infection, but have received little attention in human studies.

Lindesmith et al4 prospectively investigate a unique cohort of NV-infected subjects with an inactivating mutation in the gene encoding α-1,2-fucosyltransferase, an enzyme involved in HBGA synthesis. Known as "nonsecretors," such subjects have a limited repertoire of HBGAs and are naturally resistant to most NV strains, including GII.4 variants [3]. The authors carry out broad phenotypic and functional analysis of the immune response at days 8, 30, and 180 following natural infection with a GII.2 virus, focusing on both adaptive and innate immune responses. Moreover, they take advantage of the limited exposure history of this cohort to interrogate the cross-reactivity of GII.2-specific T cells against GII.4 virus-like particles. Because most adults have had multiple NV exposures, this is a clever approach to address the issue of preexisting versus cross-protective immunity. Lastly, the authors investigate why nonsecretors are susceptible to GII.2 infection even though these viruses fail to bind HBGAs in vitro.

The findings presented here suggest broad immune activation following acute NV infection. Like serologic responses, cellular responses vary considerably across the cohort and are even Th2-biased in 1 subject. Given the small size of this cohort and the absence of preinfection data (the authors used an independent cohort of healthy donors for comparison), there are limitations to the interpretation of the results [4]. Nevertheless, this is a comprehensive first attempt at broadly characterizing the immune response following natural NV infection. Importantly, T cells elicited by the GII.2 virus were cross-reactive against GII.4 virus-like particles, suggesting that such cells may target conserved epitopes and provide broad protection, a finding with important implications for vaccine design. Finally, in line with recent discoveries, the authors show that bile is necessary for GII.2 attachment to nonsecretor HBGAs [5].

Developing an effective NV vaccine will be facilitated by a detailed understanding of immune correlates of protection. This study is a step in the right direction, and a reminder of the challenges inherent in human NV research. Samples from larger human cohorts, preferably pre- and post-NV infection are needed to define the full breadth and durability of the T-cell immune response. Such studies should focus on the differentiation, functionality, and tissue localization of NV-specific T cells, particularly within the intestine [6]. To that end, recent efforts to map HLA-restricted NV epitopes are noteworthy, because such knowledge could enable the tracking of virus-specific T cells at baseline and following infection or vaccination.

## Basic Virology and Viral Diversity

The Norwalk virus agent (the original prototype virus is referred to as Norwalk virus in this review) was originally visualized by using immunoelectron microscopy, revealing 27-nm virus-like particles. Efforts to cultivate the pathogen in cell culture and to develop an animal model were unsuccessful; therefore, the evolving literature focused on describing the physical characteristics of this small, round-structured virus in clinical specimens and on the serologic response to infection. Although virion morphology, as well as protein and nucleic acid composition, was similar to that of members of the Caliciviridae family, clear taxonomic classification was not achieved until the whole genome sequence was obtained and compared to sequences from other caliciviruses.

The Caliciviridae family of small, nonenveloped, positive-stranded RNA viruses is now comprised of five genera, including Norovirus, Sapovirus, Lagovirus, Nebovirus, and Vesivirus [7]. The Norovirus and Sapovirus genera contain the human enteric viruses of the same names as well as a number of viruses that cause primarily enteric diseases in other animals, such as murine and canine noroviruses.

The human norovirus genome is composed of a linear, positive-sense RNA that is ~7.6 kb in length. The genome is covalently linked to the viral protein genome (VPg) at the 5′ end and polyadenylated at the 3′ end. There are three open reading frames (ORFs), designated ORF-1, ORF-2, and ORF-3, encoding eight viral proteins. ORF-2 and ORF-3 encode the structural components of the virion, viral protein 1 (VP1) and VP2, respectively. The mature virion contains 90 VP1 dimers assembled with icosahedral symmetry and arranged in such a

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fashion as to create hollows or cup-like structures on the virus surface [8]. Hence, calici is derived from the Latin word calyx, or "cup". ORF-1 encodes a polyprotein that is proteolytically processed into the 6 nonstructural proteins, including the norovirus protease and RNA-dependent RNA polymerase.

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