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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Crossing the T's on Norovirus

Human noroviruses (NoVs) are highly contagious viral pathogens and the leading cause of virally induced gastroenteritis across all age groups.[1] Currently, there are no approved therapeutics or vaccines available against NoVs. Adaptive immune control of NoVs in humans, especially humoral antibody responses, has been intensively analyzed in clinical settings, but T cell responses against NoVs have generally been understudied. NoV vaccine design has predominantly focused on antibody-mediated protection, targeting the structural portions of NoVs, but their success thus far has been limited. Recently, it was reported that antibody and cell-mediated immune responses to NoV infection have little correlation, indicating the importance of carefully tracking T cell responses and repertoire.[2] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Pattekar et al[3] survey $CD8^+$ T cell epitopes for NoV with human peripheral blood mononuclear cells from volunteers. The authors identify 7 HLA class I epitopes derived from a GII.4 pandemic stain of NoV and further confirm NoV-specific T cells in the intestinal tissue and lamina propria.

NoVs are nonenveloped, positive-stranded RNA viruses with genomes encoding 3 open reading frames (ORFs). ORF1 encodes a polyprotein precursor that is cleaved by the viral protease to make 6 nonstructural proteins, whereas ORF2 and ORF3 encode the major capsid protein, VP1, and the minor capsid protein, VP2, respectively. The protruding (P) domain of VP1 mediates attachment and entry into host cells and is the primary target of neutralizing antibodies, and of most NoV vaccines currently under development. Because potential epitopes of neutralizing antibodies are typically mapped on the exposed hypervariable region, which is under strong evolutionary pressure, vaccines targeting the P domain inherently exhibit a limitation in the breadth of strains they can target. In contrast, $CD8^+$ T cells may target conserved epitopes and could offer cross-protection against a broad range of NoVs. Cellular immunity for NoV control has been clearly shown in mouse models where depletion of $CD4^+$ or $CD8^+$ T cells enables viral persistence of murine NoVs.[4,5]

Pattekar et al[3] use a NoV peptide library and HLA-typed human peripheral blood mononuclear cells from 3 healthy donors, including a nonsecretor, to identify 7 immunodominant $CD8^+$ T cell epitopes. Three of them are in the ORF1-polyprotein, and the other 4 are in VP1. None of the 7 epitopes is on the hypervariable region, but are instead highly conserved across all variants in the same GII.4 genotype clinical isolates. Development of HLA-peptide tetramers, multimers capable of engaging more than 1 copy of the T cell antigen-receptor on the surface of a T cell, subsequently permitted the authors to analyze NoV-specific T cells across multiple donors by flow cytometry. These analyses reveal high degrees of interindividual variation in tissue distribution and phenotypes of these T cells, while simultaneously confirming that they are likely universally present among human adults. Although the sample size is limited, phenotypic functional analysis shows that NoV-specific central memory T cells and effector memory T cells are consistently polyfunctional without features of T-cell exhaustion, suggesting a pervasive capacity for individuals to mount effective T cell–mediated antiviral responses.

This study is an important addition to a currently emerging body of literature interrogating T cell responses in NoV infection.[6] Ultimately, careful characterization of how protective T cell responses develop after natural or experimental NoV infection, leveraging the tetramers newly developed by Pattekar and colleagues[3] or similar reagents, will be a critical addition to the understanding of the true correlates of immune protection. Similarly, further exploration of the role of defective T cell responses in chronic NoV infection, either in immunocompromised or immunocompetent individuals, may facilitate development of effective adoptive T cell therapies.[6] Finally, vaccine therapies focused on targeting these conserved T cell epitopes may yield broadly efficacious protection from NoV in the future.

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