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GASTROINTESTINAL NOROVIRUS INFECTIONS AND THE DEVELOPMENT OF THE NEXT GENERATION OF MUCOSAL VACCINES

Akademisk avhandling

Som för avläggande av medicinedoktorsexamen vid Sahlgrenska akademin,
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Avhandlingen baseras på följande delarbeten

I. Parveen N, **Rimkute I**, Block S, Rydell G, Midtvedt D, Larson G, Hytönen, V, Zhdanov VP, Lundgren A and Höök F. *Membrane Deformation Induces Clustering of Norovirus Bound to Glycosphingolipids in a Supported Cell-Membrane Mimic*. Journal of Physical Chemistry Letters, 2018 May 3;9(9):2278-2284.

II. **Rimkute I**, Ståhlman M, Tenge V, Lin SC, Haga K, Atmar RL, Estes MK, Lycke N, Thorsteinsson K, Bally M, Nilsson J, and Larson G. *Structural characterization of lipids and sphingolipids in human intestinal enteroids relates histo-blood group antigens of glycosphingolipids to cell permissiveness to human norovirus infection.* Manuscript.

III. Nilsson J, **Rimkute I**, Sihlbom C, Tenge V, Lin SC, Atmar RL, Estes MK, and Larson G. *Glycoproteomic analyses of individually established Human Intestinal Enteroids varying in histo-blood group status and susceptibility to human GII.4 norovirus infection.* Manuscript.

IV. **Rimkute I**, Nasir W, Schön K, Vorontsov E, Larson G, Lycke N. *Designing a novel mucosal vaccine against human norovirus infections based on a cholera toxin adjuvanted platform.* Manuscript.

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Abstract

Human norovirus (HuNoV) is the causative agent of the winter vomiting disease and the leading cause of outbreaks of gastrointestinal infections across all settings and age groups in the world. The virus is highly contagious making outbreaks difficult or often impossible to control and having a high impact on societal costs and resources. Therefore, there is a high urge for the design and development of a HuNoV vaccine. Since research on HuNoV biology and pathogenesis has been hampered by the inability to infect and efficiently propagate the virus in cell cultures, HuNoV receptor studies that address antibody-mediated protection against HuNoV have not been possible. However, such a model has recently been developed. This thesis has focused on two crucial steps towards the development of a novel mucosal subcomponent HuNoV vaccine. The first was to identify membrane components carrying histo-blood group antigens (HBGAs) that are required for HuNoV infection in the epithelial cells of the human intestine, represented as cultures of human intestinal enteroids (HIEs). The second step was to identify highly immunogenic peptides from the HuNoV capsid for generating a subcomponent vaccine that stimulates strong and long-lasting HuNoV-specific immune responses. The key findings have advanced our basic knowledge on the lipid, glycolipid and glycoprotein composition of HIEs, established from jejunal biopsies of individuals with different ABO, secretor and Lewis status. These components may all be of importance for understanding the pathogenesis of HuNoV gastrointestinal infection, as well as contribute in designing a mucosal subcomponent vaccine against HuNoV effectively preventing future HuNoV disease and outbreaks.

Keywords: human norovirus; gastrointestinal infection; mucosal vaccine; subcomponent vaccine; human intestinal enteroids; histo-blood group antigens; lipidomics; glycoproteomics; glycosphingolipids.

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