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Glycan-dependent viral infection in infants and the role of human milk oligosaccharides

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Glycan interactions play a crucial role in the infection of rotavirus (RV), norovirus (NV) and human immunodeficiency virus (HIV) as they facilitate viral attachment to the host receptor cell. A number of cell surface glycan epitopes involved in this process have been identified, including human blood group antigens (HBGAs). These antigens are also found on human milk oligosaccharides (HMO), an abundant and structurally diverse component in human milk. Breast-fed infants seem to have a reduced risk of acquiring RV, NV and HIV infection, suggesting a potential effector function of milk oligosaccharides in viral pathogenesis. However, the underlying mechanisms of HMO in viral protection and the identification of individual, structurally distinct effective HMO, needs further elucidation.

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Introduction

Viral infections are a common threat to infants especially under the age of 5. Infants are repeatedly challenged by diarrhea-causing viruses such as rotavirus (RV) and norovirus (NV) that are responsible for up to 70% of acute gastroenteritis episodes [1]. In addition, human immunodeficiency virus (HIV) infection is observed in breast-fed children of HIV-positive mothers [2].

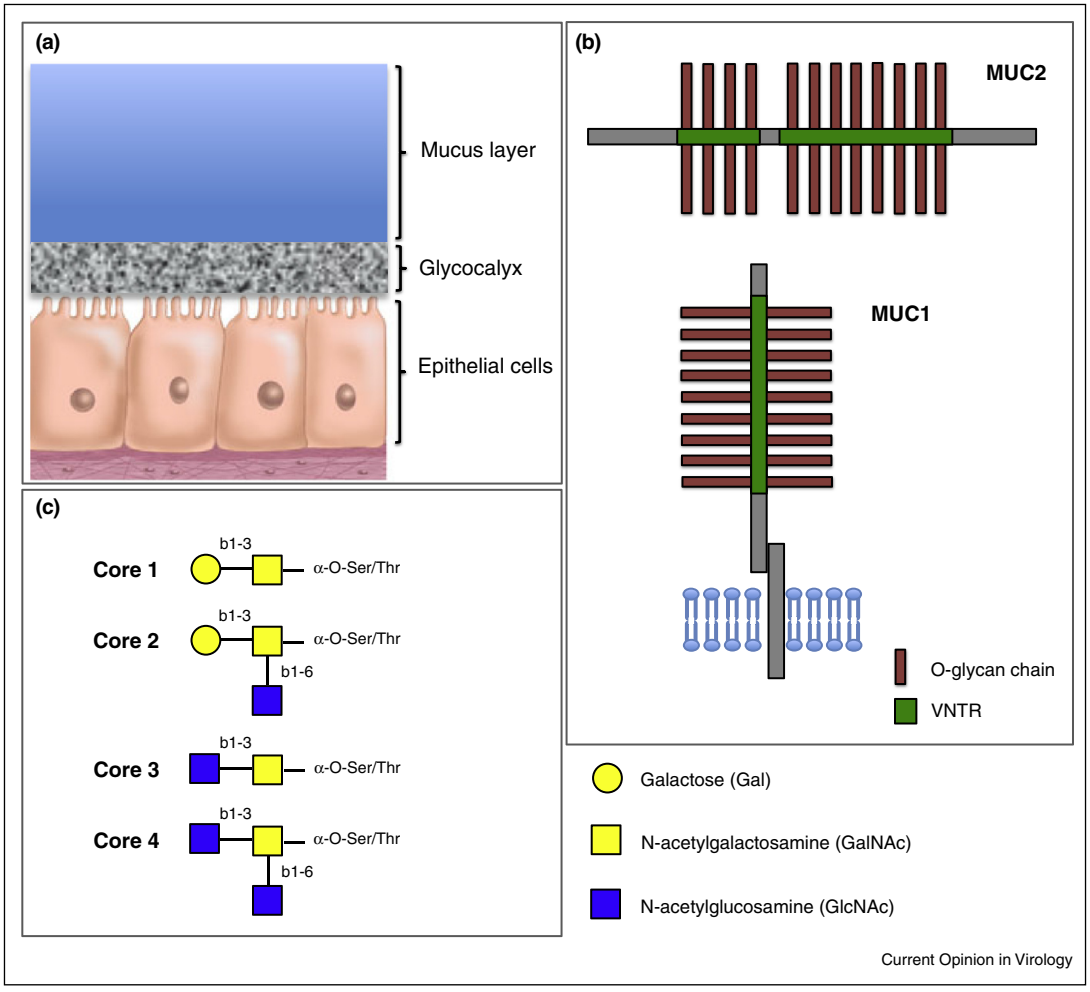
RV and NV are the two major causative agents of acute gastroenteritis worldwide in children and responsible for up to 300,000 and 110,000 deaths globally in children under the age of 5, respectively [3]. 95% of all children in the US had a case of RV infection before the age of 5 [4]. After introduction of RV vaccines in 2006, NV has become the leading cause of acute gastroenteritis in children under the age of 5 in the US [5,6]. More than 500,000 children became infected with HIV in 2006 and an estimated number of 2–3 million children worldwide are HIV-infected (UNAIDS/WHO AIDS epidemic update: Dec 2006). 40% of all HIV-infections in children are caused by mother-to-child transmission and breast-feeding remains the most common route for pediatric HIV-infection with a transmission rate of about 10–15% [2,7].

Glycans in the gastrointestinal (GI) tract

RV, NV and HIV virus attachment to host surfaces is a crucial first step in establishing viral infection and is mediated via specific carbohydrate dependent virus–host receptor interactions including the recognition of glycans such as human blood group antigens (HBGAs) [8,9,10•,11]. HBGAs, including ABO and Lewis histo-blood group antigens, are expressed as part of glycoconjugates on the cell surface of red blood cells and epithelial cells at mucosal surfaces [12].

In the mucosal surface of the gastrointestinal (GI) tract, these epitopes, among other glycan structures, can be found both in the glycocalyx, the carbohydrate rich cell surface layer, and the secreted mucus layer covering the intestinal epithelium (Figure 1a). Both polysaccharide coatings contribute to the mucosal barrier and especially the mucus layer provides attachment sites for intestinal microbes [13]. Glycans of the glycocalyx are associated with the cell membrane and are lipid-bound or protein-bound, and can mainly be found on cell-surface bound mucin glycoproteins, such as MUC1, MUC3 or MUC4 [14]. By contrast, the secreted mucin MUC2 is the main structural component of intestinal mucus and contributes to its viscous mesh-like properties, as the protein polymerizes at its C-termini and N-termini [15]. Mucins are characterized by variable numbers of tandem repeats (VNTRs) located in the central region of the proteins (Figure 1b). These sequence repeats are rich in Serine (Ser) or Threonine (Thr) residues, the sites of protein O-glycosylation, while only comparably few N-glycosylation sites are present at the proteins' N-termini and C-termini. The majority of mucin O-glycans are built upon the four most common core structures (core 1–4) (Galβ1,3GalNAc-Ser/Thr; Galβ1,3[GlcNAcβ1,6]GalNAc-Ser/Thr; GlcNAcβ1,3GalNAc-Ser/Thr; GlcNAcβ1,3[GlcNAcβ1,6]GalNAc-Ser/Thr: galactose (Gal), N-acetylgalactosamine (GalNAc), N-acetylglucosamine (Glc)) (Figure 1c)

Figure 1



Structural components of the intestinal epithelial cell surface. **(a)** Schematic presentation of the mucosal cell surface. **(b)** Gel-forming and cell-surface mucins MUC2 and MUC1, respectively. **(c)** O-glycan core types 1–4 common in mucins.

[16]. These core types can be further elongated with Gal or GlcNAc monosaccharides followed by modification with differentially linked fucose (Fuc) or sialic acid (Sia, Neu5Ac, N-acetylneuraminic acid) to form distinct glycan epitopes. Glycan determinants described for intestinal MUC1 and commonly encountered at the intestinal epithelial cell surface are the ABO antigens A and B, and the Lewis antigens Le^x and Le^y [12,17]. Regio-specific expression of the ABO antigens H and A, as well as Le^a, Le^b and Le^x has also been demonstrated for the gel-forming MUC2 in different parts of the intestine [18,19]. Furthermore, glycan structures carrying terminal Sia have been identified on MUC2 either alpha2,3 linked to Gal or alpha2,6 linked to GlcNAc [18].

HBGAs found at the intestinal mucosal surface are also present as unconjugated glycans in human fluids including human milk. These human milk oligosaccharides (HMO) are the third most abundant component of human milk (5–15 g/L) and a complex mix of over 150 structurally distinct glycans. HMO resists the low pH of the infant's stomach and enzymatic digestion after ingestion [20,21]. They reach the distal small and large intestine in an intact form, where a number of them, especially longer HMO, then undergo hydrolysis and processing before excretion with the infant's feces [21–23]. Additionally, *in vivo* labeling studies showed that HMO are absorbed in the infant's intestine, reach the systemic circulation and about 1% can be found in the urine of breast-fed infants [24].

Common glycan epitopes in viral infection

HBGAs, whose expression is genetically determined, have been identified as host receptors for RV and NV attachment [9,25] and play a role in preventing HIV attachment [26]. The common building block of HBGAs is a type 1 (Galβ1,3GlcNAc) or a type 2 (Galβ1,4GlcNAc) N-acetyllactosamine (LacNAc). It can be further