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# Structural features of glycan recognition among viral pathogens

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Recognition and binding to host glycans present on cellular surfaces is an initial and critical step in viral entry. Diverse families of host glycans such as histo-blood group antigens, sialoglycans and glycosaminoglycans are recognized by viruses. Glycan binding determines virus–host specificity, tissue tropism, pathogenesis and potential for interspecies transmission. Viruses including noroviruses, rotaviruses, enteroviruses, influenza, and papillomaviruses have evolved novel strategies to bind specific glycans often in a strain-specific manner. Structural studies have been instrumental in elucidating the molecular determinants of these virus–glycan interactions, aiding in developing vaccines and antivirals targeting this key interaction. Our review focuses on these key structural aspects of virus–glycan interactions, particularly highlighting the different strain-specific strategies employed by viruses to bind host glycans.

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## Introduction

Viruses recognize and bind host glycans as cell attachment factors, receptors or co-receptors, as a prerequisite for viral entry and subsequent infection [1]. Viruses exhibit a remarkable degree of selectivity and specificity while also evolving strain-specific strategies to engage host glycans. Glycan-binding can dictate virus–host specificity, tissue tropism, pathogenesis and interspecies transmission. Viruses predominantly recognize three distinct families of host glycans including: histo-blood group antigens (HBGAs) recognized by noroviruses (NoVs) [2] and human rotaviruses (HRVs) [3]; sialoglycans recognized by influenza viruses [4], orthoreoviruses [5] and specific picornaviruses [6,7]; and glycosaminoglycans (GAGs) recognized by papillomaviruses [8] and parvoviruses [9] among others. Understanding virus–glycan interactions is critical, as blocking this interaction using glycomimetics or antibodies can lead to reduced virus infectivity and targeting these interactions can lead to the development of antivirals and vaccines.

## Recognition of HBGAs by gastroenteric viruses

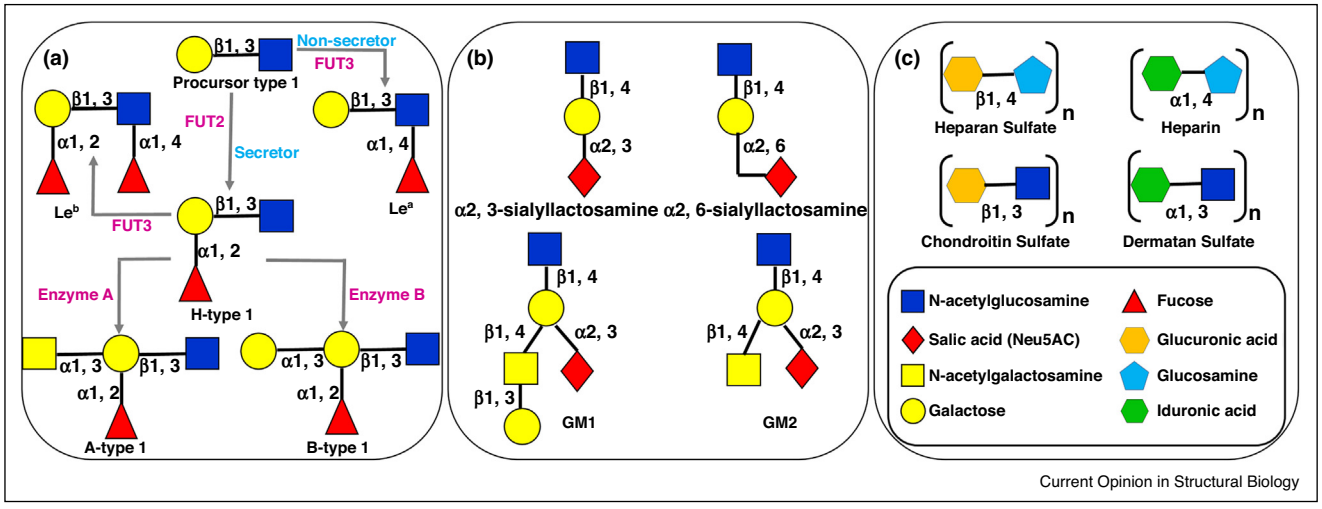
HBGAs are genetically determined neutral glycans expressed on the surface of intestinal epithelial cells, and found in mucosal secretions of individuals. These polymorphic group of glycans are synthesized by the sequential addition of monosaccharide units onto a precursor disaccharide (Figure 1a). Two HBGA families, the ABH and Lewis family, are implicated in binding to viruses [10,11]. HBGA binding by the two leading causes of viral gastroenteritis, NoVs and HRVs is discussed below.

## HBGA recognition by human NoVs

NoVs are non-enveloped positive-sense ssRNA viruses belonging to *Caliciviridae*. They are classified into 7 genogroups (GI–GVII) of which genogroups GI, GII, and GIV cause infections in humans [12]. Each genogroup is subdivided into multiple genotypes. The prototype Norwalk virus (NV) belongs to genogroup I, genotype 1 (GI.1). Genotype GII.4 is the globally dominant genotype [13], but recently GII.17 strains emerged as a predominant genotype in parts of Asia [14]. Differential strain-specific HBGA binding along with antigenic drift drives the evolution of NoVs.

NoVs recognize HBGAs as susceptibility [15] and cell attachment factors through the P-domain of their capsid protein VP1 [16–18]. Interestingly, HBGA bound P-domain structures from GI and GII NoVs show that the HBGA binding sites are distinct in both location and structural characteristics between these two genogroups (Figure 2a) [17,19]. The mode of HBGA binding is also distinct, with the GI strains primarily binding to the galactose (Gal) of the disaccharide precursor (Figure 2b), and the GII strains binding to the fucose (Fuc) moiety of the HBGA (Figure 2c). Closer examination of the HBGA

**Figure 1**




Schematic representation of the diverse cellular glycans recognized by viruses: **(a)** Polymorphic HBGAs: HBGA synthesis starts with a common disaccharide precursor. The glycosidic linkage and composition of this precursor disaccharide determines the HBGA types (type 1- 4). Shown here are the type 1 (with β 1, 3 linkage in the precursor) HBGAs. Similarly, type 2 HBGAs have β 1, 4 linkage. Sequential addition of monosaccharides to this disaccharide precursor by various fucosyl (FUT2, FUT3) and glycosyltransferases (Enzyme A and B) results in FUT2-dependent secretor ABH and Lewis HBGAs, and in the absence of functional FUT2, results in nonsecretor Lewis types of HBGAs. **(b)** Representative sialoglycans: The commonly expressed sialoglycans recognized by viruses are shown and though sialoglycans with internal SA moieties are also recognized, only sialoglycans with terminal SA moieties are depicted. **(c)** Representative glycosaminoglycans: GAGs are long unbranched polysaccharides with repeating disaccharide units of sulfated glycans including iduronic and glucuronic acid. The disaccharide repeats of the GAGs that are commonly recognized by viruses are depicted.

binding site reveals that there are two subsites involved in HBGA binding. A conserved primary site (site 1), binding either the Gal residue in GI or the secretor-Fuc in GII, and a secondary evolving site (site 2) that is susceptible to sequence and structural alterations, allowing strain-specific HBGA binding [18,20,21] (Figure 2b, c). Site 2 in GII.4 variants identified post-2002 have evolved the ability to bind non-secretor Lewis HBGAs, and that might explain the prevalence of these variants [18].

Serum antibodies that bind NoVs and block HBGA binding are correlates of protection against NoV gastroenteritis [22]. Recently the structure of one such human antibody in complex with the NV P-domain was determined and it revealed steric hindrance as the mechanism of HBGA blockade [23]. Other structural studies have shown that human milk oligosaccharides, 2′-fucosyllactose (2′L) and 3′-fucosyllactose (3′FL) and molecules like citrate mimic HBGA binding, thus serving as decoy receptors and potential glycomimetics [24,25].

## HBGA recognition by human RVs

While HBGA binding in human NoVs is well characterized, the HBGA binding among HRVs is a recent emerging paradigm shift that diverges from the sialoglycan binding observed in animal rotaviruses (ARVs) [26]. Recent epidemiological studies show that secretor-positive individuals are significantly more susceptible to HRV infections suggesting that HBGAs are susceptibility factors for HRV infection similar to human NoVs [27].

RVs are non-enveloped multi-segmented dsRNA viruses belonging to *Reoviridae*. To date, they are classified into 32 G genotypes and 47 P genotypes based on their two antigenic outer capsid proteins, glycoprotein VP7 and protease-sensitive VP4, respectively [28,29]. VP4 is cleaved into VP8* and VP5*, with VP8* involved in glycan recognition. The structure of VP8* comprised of two twisted β-sheets separated by a shallow cleft resembles the galectin-like fold and is conserved among RVs (Figure 2d).

HRVs were recently shown to bind HBGAs. A P[14] HRV strain, with origins in even-toed ungulates, specifically binds A-type HBGA within a narrow cleft between the two β sheets (Figure 2d) [3]. The A-type HBGA binds to P[14] VP8* in a similar location as the sialic acid (SA) in the ARV VP8* (Figure 2d). The determinant of this receptor switch is an insertion of a residue serine 187 in P[14] VP8* that reorients the sidechain of a neighboring residue tyrosine 188 such that it sterically blocks access to SA while engaging in hydrophobic interactions with A-type HBGA (Figure 2e). Further, the presence of A-type HBGA in both even-toed ungulates and humans provides the basis for potential interspecies transmission of this genotype. More recently, structural studies on VP8* of a neonatal bovine-human reassortant P