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Norovirus, glycans and attachment

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Noroviruses engage glycans as essential attachment factors to promote infection of host cells. The past decade has witnessed significant progress in the field of norovirus research. Cell culture systems and animal models have become available, and structural biology and biophysics have significantly expanded our understanding of norovirus–glycan interactions. From crystallography, many high-resolution crystal structures are now available disclosing key elements of glycan recognition at atomic resolution. On this basis, NMR spectroscopy, native mass spectrometry, and biophysical techniques targeting membrane attached glycans have raised more intricate questions about the nature of norovirus–glycan attachment implying that a static picture of glycan recognition is insufficient. Linking novel biophysical observations to biological aspects of norovirus host cell entry is a challenge. Therefore, in a first step, this review summarizes and discusses recent biophysical approaches potentially paving the way to a dynamical picture of norovirus-glycan attachment. Novel insights from norovirus–glycan binding studies are put into perspective with current general developments in the field of protein–glycan interactions, hopefully provoking new ideas for norovirus research.

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Introduction

Noroviruses belonging to the family of *Caliciviridae* are subdivided into seven genogroups GI-GVII, and into more than 30 genotypes, of which only genogroups GI, GII and GIV are known to infect humans [1]. Human noroviruses (HuNoV) are known to interact with Lewis and histo blood group antigens (HBGAs), and these interactions are thought to be important for infection. However, it is currently not known how binding to these glycans promotes or modulates host cell entry. A number of recent reviews address associated open questions from different perspectives [2•,3,4,5,6,7]. While HBGAs undoubtedly play an important role in the infection process, the inability to productively infect permissive cells carrying HBGA on their surface [8] and the recent discovery of a proteinaceous entry receptor for murine noroviruses (MNVs) [9•,10•] suggests that additional attachment and/or entry factors also exists for HuNoVs. The establishment of cell culture systems for HuNoVs now offers novel opportunities to study the functional role of HBGAs in norovirus infection [11,12,13•,14,15,16,17•]. These new findings support the notion that norovirus cell entry is a rather intricate process with many players involved. Future progress in the field of norovirus research will certainly depend on further advances in cell culture and animal models on the one hand, and on insights into the molecular machinery behind the infection process on the other hand. Indisputably, understanding HBGA attachment of HuNoVs on a molecular level is one important piece of this puzzle. Therefore, here we review recent findings from a variety of biophysical, and structural biology studies shining light on norovirus–glycan attachment. Using a broader perspective, norovirus–glycan attachment falls into the class of protein–carbohydrate interactions, and it is instructive to compare to other glycan binding proteins identifying common principles of molecular recognition [18•,19•,20•,21,22]. Although it is well known that carbohydrate–protein interactions are characterized by low affinities, associated recognition reactions can be of exceptional specificity. The well-studied recognition of sialyl Lewis^x epitopes by E- and P-Selectin is a prototypical case [23•] featuring most of the specific thermodynamic and structural aspects of protein–carbohydrate interactions, and especially highlighting the distinct molecular requirements for turning a carbohydrate ligand into a drug [24,25] thus providing a role model for the design of carbohydrate-based antiviral entry-inhibitors. Entry inhibition employing peptide-based inhibitors had been successfully employed in the case of HIV and is currently explored for other viruses such as Dengue or West Nile virus, where carbohydrate-based structures may also play a role [26,27,28,29]. Apparently, nature employs glycan attachment as a highly specific yet transient means to recruit complex biological entities such as cells or viruses at certain points in time to specific locations, or to hide relevant domains from immune attack. In norovirus infection, carbohydrates are operating as attachment factors transiently binding to HBGAs, and in turn likely driving