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Editorial overview: virus–glycan interactions and pathogenesis

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Virus-glycan interactions and pathogenesis

The first step in a viral infection is recognition of a cell-surface entity and binding to it in a way that triggers viral entry. For many viruses this initial binding is to glycans, often those attached to the cellular glycoproteins or glycolipids. Since interference with this initial step is likely to prevent viral infection, it is important to understand the interaction and whether it is very specific (thereby targetable by drugs) or very flexible, thereby bypassing designed antivirals.

Although simple in principle, studies on virus-glycan interactions have been difficult. Glycans are by far the most complex of biological compounds, and the spectrum of glycans expressed on a tissue surface remains unknown. Mass spectrometry is being used to study glycans of particular tissues such as human lung, but even the most powerful machines are not sensitive enough to study specifically the glycans on the epithelial surface and linkages and branches remain ambiguous. There is likely to be individual variation in glycan structures because the glycosyltransferases are highly regulated, such as during development. For these reasons, studies have focused on the virus, and in particular X-ray structural analysis of what moieties the virus can bind using libraries of synthetic glycans. The biological significance of the glycans that bind most avidly can then be investigated in vivo.

In recent years there has been an exciting progress in our understanding of the type of glycans that are specifically recognized by a variety of human viruses, in vivo relevance of this recognition process, its impact on the evolution of viruses, and the structural basis of virus-glycan interactions. This volume highlights this progress.

David Smith and Richard Cummings describe the development and use of glycan array technology to study virus-glycan interactions. New methods in both chemical and enzymatic synthesis have resulted in arrays containing over 600 glycan structures that can be used to screen the specificity or breadth of binding by viruses and viral surface proteins. Further developments will include tissue-specific arrays representing the glycans actually present in, for example, the upper or lower human respiratory tract. This special issue highlights several studies that have utilized this emerging technology.

Studies on the members of Parvoviridae provide an excellent example of the use of glycan array technology. Lin-Ya Huang, Sujata Halder and Mavis Agbandje-McKenna show that viruses in this family are remarkably consistent in their glycan recognition specificity. For these viruses, there is direct correlation between the glycan structures bound, their presence on the host cell surface, and ability to initiate a productive infection. These studies point the way to designing gene transfer vectors based on adeno-associated virus that can be targeted more effectively to specific tissues.

In recent years, there has been a significant development in our understanding of glycan specificity in oncogenic viruses such as polyomaviruses. Samantha O'Hara, Thilo Stehle and Robert Garcea discuss glycan binding by polyomaviruses, and the relationship between binding affinity and specificity to tropism and pathogenicity of the virus. This review also underscores how one or two amino acid changes in the viral attachment protein VP1 can cause major differences *in vivo* but may show little effect on *in vitro* assays.

Influenza viruses have attracted a lot of attention the past 15 years because of the emergence of new avian influenza viruses that occasionally infect humans. So far these avian viruses have not acquired the capacity to transmit between humans but it is thought that mutations that change the receptor specificity could start a new human pandemic. Gillian Air discusses binding specificity of avian and human viruses. The H3N2 viruses show drift in binding specificity from their initial entry into the human population in 1968 until the present day. Some of these human viruses bind glycans that are considered avian receptors but still were able to transmit efficiently from human to human to cause world-wide epidemics.

Gastroenteric viral pathogens such as human noroviruses and rotaviruses are rather unique in that they specifically recognize histo-blood group antigens (HBGAs), which are the genetic determinants of blood type, for initial cell attachment. While it has been long known that these glycans are susceptibility factors for human noroviruses, it is only recently that several studies have indicated the possibility that the susceptibility to human rotaviruses also depends upon the expression of these glycoconjugates. These glycans present at the surface of the small intestine are also found on human milk oligosaccharides (HMO) and they are third most abundant component of human milk. Interestingly, recent studies have highlighted the inverse relationship between the rate of HIV transmission and breastfeeding. Sabrina Etzold and Bode discuss the role of the HMO in the infection caused by gastroenteric viruses and also HIV particularly emphasizing the routes by which HMO can interfere with viral pathogenesis. Strain-dependent recognition of polymorphic HBGA by human rotaviruses and noroviruses present a fascinating case study of continuous co-evolutionary process involving both host and viruses. This is the topic of discussion in the review by Jaques Le Pendu, Kristina Nyström, Nathalie Ruvoën-Clouet, drawing from the well documented studies on the evolution of rabbit hemorrhagic disease virus, an animal calicivirus, which also bind to HBGA in the gut mucosa similar to human gastroenteric viruses. B.V.V. Prasad, Sreejesh Shanker, Liya Hu et al. review the current progress in our understanding of the structural basis for how rotaviruses and noroviruses recognize different sets of HBGA in a strain-dependent manner.

While most of the articles in this issue focus on viral lectin recognition of cell-surface glycans that act as receptors, Leonardus Koharudin and Angela Gronenborn describe a different approach, investigating the antiviral activity of cyanobacterial or algal lectins that bind high-mannose glycans of HIV gp120 and prevent the conformational changes necessary for cell entry by the virus. The authors discuss promising pre-clinical trials and also the challenges of delivery and specificity and potential ways to overcome these.

Going beyond the significance of glycan interactions in cell attachment of viruses, Nadine A Dalrymple, and Erich Mackow highlight the current status of our understanding of how viruses such as dengue viruses, Hantaviruses and arenaviruses that cause hemorrhagic disease interact with the proteoglycan receptors in the endothelial cells, and the consequence of this interaction in directing the disease by altering the endothelial cell barrier function.

Concluding remarks

The last 10 years have seen remarkable progress in understanding viral glycobiology. In particular there have been successes in synthesizing complex glycans that are used in the glycan arrays to study what structures are bound by viruses and advances in mass spectrometry to analyze glycans expressed in specific tissues that are targeted by viruses. The main problems still remaining are to identify the biologically relevant receptors that are used by viruses as opposed to the best binding glycans that have been synthesized. For some viruses there are elegant complementary studies that show the “real” receptors as described in this issue, but for others, that bind glycans that are widely distributed, the role of high affinity glycan binding in productive infection is still unclear. However, knowledge of the structure of high affinity ligands, and particularly where there are x-ray structures of ligand-virus or viral protein interactions, opens the door to design of inhibitors of virus binding that are specific and potent and that will prevent the virus from entering new cells.

We express our gratitude to all the authors who have contributed to this volume for their time and effort. We also thank the editorial staff of Current Opinion in Virology for making this volume a reality.

Biographies

BV Prasad is Alwyn Romansky Professor and Chair of Biochemistry and Molecular Biology. He has been working on the structural biology of RNA viruses including rotaviruses, noroviruses and influenza viruses, making contributions to understanding the structural basis for the capsid-related activities such as how viruses gain entry into host cells, how they interact with receptors, how they evade immune surveillance, in addition to the understanding the molecular processes by which these viruses successfully replicate once inside the host cells.

Gillian Air is George Lynn Cross Professor of Biochemistry & Molecular Biology. She has been working on influenza viruses since 1977, making contributions to understanding the mechanism antigenic drift, how influenza hemagglutinin and neuraminidase escape from antibody neutralization, development of antivirals targeting the neuraminidase, and recently studies on the surprising variation in sialic acid recognition by influenza viruses.