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Volume 790
VIRAL ENTRY INTO HOST CELLS
Stefan Pöhlmann and Graham Simmons

Viral Entry into Host Cells

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Springer Science+Business Media, LLC, 233 Spring Street, New York, New York 10013, USA
http://www.springer.com

Please address all inquiries to the publishers:
Landes Bioscience, 1806 Rio Grande, Austin, Texas 78701, USA
Phone: 512/ 637 6050; FAX: 512/ 637 6079
http://www.landesbioscience.com

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Viral Entry into Host Cells, edited by Stefan Pöhlmann and Graham Simmons. Landes Bioscience / Springer Science+Business Media, LLC dual imprint / Springer series: Advances in Experimental Medicine and Biology.

ISBN 978-1-4614-7650-4

Library of Congress Cataloging-in-Publication Data

Viral entry into host cells / edited by Stefan Poehlmann, Graham Simmons.
p. ; cm. -- (Advances in experimental medicine and biology ; v. 790)
Includes bibliographical references and index.
ISBN 978-1-4614-7650-4 (alk. paper)
I. Poehlmann, Stefan, 1970- II. Simmons, Graham, Ph. D. III. Series: Advances in experimental medicine and biology ; v. 790.
[DNLM: 1. Virus Internalization. 2. Endocytosis. 3. Host-Pathogen Interactions. QW 160 / W1 AD559 v.790 2013]
QR201.V55
571.9'92--dc23

2013013131

PREFACE

For a virus to invade a host cell it needs to penetrate the physical barrier imposed by the plasma membrane. Viruses have evolved specialized surface proteins to meet this challenge. These proteins facilitate delivery of the viral genetic information into the host cell by either fusing the viral envelope with a host cell membrane (enveloped viruses) or by forming membrane pores (non-enveloped viruses). Membrane fusion and pore formation critically depend on the engagement of host cell receptors and receptor choice is a key determinant of viral tropism. The multi-faceted interplay between viral and cellular factors during virus entry is a fascinating field of study, which can provide important insight into viral pathogenesis and define new targets for intervention. This book provides a comprehensive overview of this exciting field of research.

The first step in viral entry is the attachment of virions to target cells. Cellular factors which promote viral attachment and their role in virus infection are reviewed by Jolly and Sattentau. Two chapters review key processes underlying host cell entry of non-enveloped viruses: Bergelson and Coyne discuss the cell biology of picornavirus entry. These viruses exploit various endocytic pathways to invade cells and, by binding to cell surface receptors, activate signaling cascades which prime the cells for infection. Cellular entry of reoviruses is discussed by Danthi and colleagues. Members of the reovirus family depend on the cellular proteases cathepsins B and L for disassembly and viral structures exposed during disassembly can induce signaling cascades, which drive cells into apoptosis.

Enveloped viruses have evolved three related yet distinct solutions to bind and enter target cells: Class I, II and III membrane fusion proteins. Class I membrane fusion proteins are discussed in four chapters. Sun and Whittaker introduce the prototype class I membrane fusion protein, the influenza virus hemagglutinin. Simmons discusses entry of Ebola and Marburg virus, the only members of the filoviridae family. These viruses enter an extremely broad range of cells in a pH-dependent fashion. However, the pH-dependence is indirect: An acidic milieu is required for the activity of cathepsins B and L, which prime the viral glycoprotein for membrane fusion. A particular solution to host cell entry has been evolved by paramyxoviruses, which encode two distinct proteins to accomplish attachment to host cells and membrane fusion. Bossart and Broder describe

how these proteins cooperate during host cell entry. Retroviruses comprise important human pathogens and are frequently used to study virus-host interactions during entry. Lindemann and colleagues review how foamy virus and HIV select and enter target cells. Class II membrane fusion proteins are structure- and sequence-wise different from class I fusion proteins but employ related mechanisms to merge the viral and cellular membranes. The key features of class II membrane fusion proteins are discussed by Modis. Class III membrane fusion proteins combine elements of the other classes and are only found in herpes-, rhabdo- and baculoviruses. Regan and Whittaker guide the reader through each step of host cell entry of rhabdoviruses. Entry of herpes viruses into host cells is facilitated by several viral glycoproteins and is regulated by glycoprotein-glycoprotein and glycoprotein-receptor interactions. The respective processes are reviewed by Krummenacher and colleagues, with a particular focus on the structures involved in receptor binding.

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ACKNOWLEDGMENTS

The editors are very deeply indebted to all chapter authors for their excellent contributions, support and patience. We are particularly grateful to the authors of chapter updates. We are also thankful to Celeste Carlton and Cynthia Conomos at Landes Bioscience for their support and patience.

CHAPTER 1

ATTACHMENT FACTORS

Clare L. Jolly and Quentin J. Sattentau*
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Abstract: As obligate intracellular parasites, viruses must bind to, and enter, permissive host cells in order to gain access to the cellular machinery that is required for their replication. The very large number of mammalian viruses identified to date is reflected in the fact that almost every human and animal cell type is a target for infection by one, or commonly more than one, species of virus. As viruses have adapted to target certain cell types for their propagation, there is exquisite specificity in cellular tropism. This specificity is frequently, but not always, mediated by the first step in the viral replication cycle: attachment of viral surface proteins to receptors expressed on susceptible cells. Viral receptors may be protein, carbohydrate, and/or lipid. Many viruses can use more than one attachment receptor, and indeed may sequentially engage multiple receptors to infect a cell. Thus, it is useful to differentiate between attachment receptors, that simply allow viruses a foothold at the limiting membrane of a cell, and entry receptors that mediate delivery the viral genome into the cytoplasm. For some viruses the attachment factors that promote binding to permissive cells are very well defined, but the sequence of events that triggers viral entry is only now beginning to be understood. For other viruses, despite many efforts, the receptors remain elusive. In this chapter we will confine our review to viruses that infect mammals, with particular focus on human pathogens. We do not intend that this will be an exhaustive overview of viral attachment receptors; instead we will take a number of examples of well-characterized virus-receptor interactions, discuss supporting evidence, and highlight any controversies and uncertainties in the field. We will then conclude with a reflection on general principles of viral attachment, consider some exceptions to these principles, and make some suggestion for future research.

Viral Entry into Host Cells, edited by Stefan Pöhlmann and Graham Simmons.

INTRODUCTION

Despite striking differences in genome type, replication, morphology and tropism, all viruses carry structures, usually proteins, on the outer surface of the virion that mediate attachment to receptors expressed on the surface of target cells. There are two principal groups of viruses, with gross classification based on whether they are limited by a lipid membrane derived from a host cell membrane (enveloped viruses), or nonenveloped viruses, that have a protein exterior. Although most examples of viral surface structures are virally-encoded, others, such as adhesion molecules and proteoglycans, may be host cell-derived.

Attachment may be a relatively nonspecific process, by which surface viral structures associate reversibly with the cell limiting membrane via generalized biochemical properties such as charge, or may use more sophisticated bonding patterns to receptors that are specific for the viral family, genus, type, subtype or strain. A number of viruses use ubiquitously expressed receptors to attach to target cells, and replication is restricted by other factors, for example temperature sensitivity in the case of viruses that target the upper respiratory tract. Glycoproteins are major targets for viral attachment, and due to their regulated expression on different cell types, help provide the specificity required for viral tropism. Lipids are also used by a number of viruses for binding to target cells, particularly viruses that invade cells of the gastrointestinal tract. A great many viruses take advantage of the carbohydrate moieties present on both glycoproteins and glycolipids.

Because receptor binding is the essential first step in viral replication, and most viral attachment receptors are nonpolymorphic, there is strong selective pressure to maintain highly conserved receptor binding sequences. This is in the face of negative selective pressures such as those exerted by neutralizing antibodies. To overcome this, some viruses have adapted to shield the important receptor binding domains of their protein using a variety of strategies including protective glycan 'shields' and protein 'decoys'. Another strategy is to bury the receptor binding surface in a cleft or 'valley', occluding bulky immunoglobulin molecules. Furthermore, a number of viruses have evolved to use conformational changes, triggered by binding to a primary attachment receptor, to expose or create a previously hidden or 'cryptic' domain that then attaches to a second receptor, commonly the one that then mediates virus entry into the cell. For some viruses these interactions are very well defined, and contact sites have been mapped precisely to specific amino acid residues on the viral attachment protein, interacting with known domains on the cognate cellular receptor. Two very good examples of viruses where a great deal is known about the mechanism of virion attachment are the human immunodeficiency virus (HIV) and influenza A virus. Both of these viruses have benefited from intense study over a number of years and unparalleled levels of structural and functional information are available.

NONSPECIFIC VIRUS-RECEPTOR INTERACTIONS

Charge-Based Interactions

Often, viruses may find themselves in conditions that are unfavourable for cellular attachment, examples of which include the presence of competitive ligands in the extracellular milieu, conditions of flow such as are found in the vasculature, and repulsive

forces of viral and cellular membranes in the case of enveloped viruses. Virus particles are often relatively labile, and inactivation of infectivity may ensue if entry into a cell is not achieved relatively rapidly. Thus, viruses need to limit random three-dimensional diffusion and expedite the receptor engagement process. To achieve this, many have chosen to anchor onto the cell glycocalyx, as this is the first physical structure to be encountered as the cell surface is approached. The glycocalyx is a ubiquitous carbohydrate 'umbrella', that contains negatively charged moieties in which the charge density is dependent on cell type and stage of differentiation and maturation. The charge within the glycocalyx is predominantly contributed by a group of glycoproteins called proteoglycans, that express sulfated glycan side chains termed glycosaminoglycans (GAGs). The number of glycan chains and the degree of sulfation varies according to the proteoglycan type, resulting in a wide spectrum of charge densities per molecule (Fig. 1). Moreover, the composition of the repeating dissacharide units allows for many different sulfated proteoglycans to exist, of which heparan sulfate and to a lesser extent, chondroitin sulfate can serve as viral attachment factors.

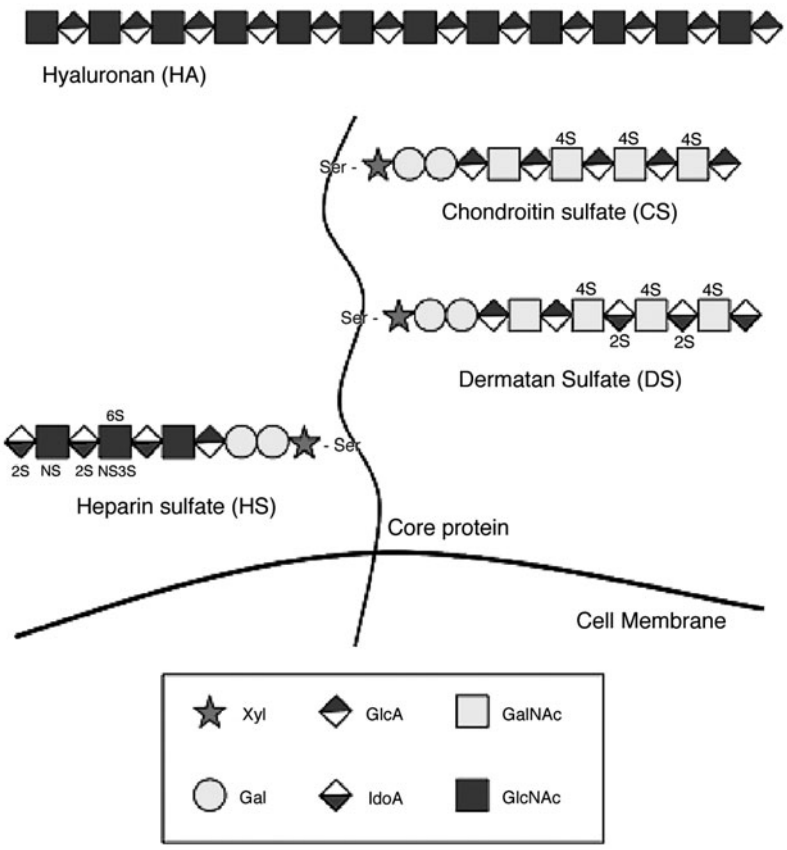

Figure 1. Schematic illustration of the composition of the major glycosaminoglycan side chains. Many viruses use HSPGs to attach to target cells and there is evidence that a select few may also associate with chondroitin sulfate containing proteoglycans.

A variety of both eukaryotic and prokaryotic pathogens, including viruses, bacteria, fungi and parasites have the ability to associate with proteoglycans. The requirement for proteoglycan binding appears to be a somewhat indistinct motif or patch of basic amino acids on the pathogen surface, but there is a degree of specificity linking the structure and charge of the pathogen motif and the type of proteoglycan used. GAGs are very promiscuous attachment receptors for viruses: many viruses have been identified that bind GAGs, including member of the *Retroviridae*, *Picornaviridae* and *Flaviviridae*[1-6] (Table 1), and the list is growing.

HSV

The first described and one of the best-characterized virus-proteoglycan interactions is probably that between herpes simplex virus type 1 (HSV-1) and a class of highly sulfated proteoglycans termed heparan sulfate proteoglycans (HSPGs). Herpes simplex virus attachment and entry into target cells requires the concerted action of multiple viral glycoprotein and cellular receptors, but the attachment of virions to permissive cells is initiated by binding of the viral structural proteins gB and gC to the disaccharide repeats of heparan sulphate.[7,8] In vitro, this association probably concentrates virions on the surface of target cells and facilitates subsequent interactions between HSV-1 glycoproteins and cellular receptors that are required for virus entry. Binding of gB or gC to HSPGs alone is insufficient to mediate virus entry, but in the absence of gC, infection decreases 10 fold,[9] and although HSPG binding is not an absolute requirement for virus entry the increased kinetics of infection after HSPG binding means they function as true attachment receptors. The recognition events that permit gB and gC to bind heparan sulfate are currently being dissected and it appears the minimal oligosaccharide recognized by HSV comprises as little as 10 monosaccharide units.[10] Interestingly, data indicate that gB and gC do not recognize the same receptor unit, moreover different gC proteins from different HSV types (HSV-1 versus HSV-2) also attach to distinct receptor domains,[11,12] however the importance of this in vivo is not established. Of the two HSV-1 glycoproteins that interact with HSPGs, gC may be more important in initial attachment, and while it is dispensable for growth in vitro, it is almost always expressed in primary patient isolates (reviewed in ref. 13). Within gC the basic and hydrophobic amino acids between 129 and 160, and residue 247, interact with heparan sulfate; mutation of these residues significantly reduces attachment of virions to cells.[14] This is consistent with the idea that positively charged viral domains promote binding to negatively charged heparan sulfate disaccharides. As mentioned earlier, there is some redundancy in the system and although the presence of gC enhances infectivity measurably, both gB and gC can bind to heparan sulfate. Mutation studies have shown if both proteins are removed, virus infectivity is severely impaired, however interpretation of these data is complicated because gB has a role in virus entry that is independent of the initial HSPG binding.[15] Although the relative contributions of gB and gC to virion binding are difficult to dissect, clearly the maintenance of both gB and gC in HSV-1 evolution indicates these proteins are indispensable for viral infectivity and pathogenesis.

As well as interacting with heparan sulfate containing GAGs, there is evidence that HSV can use chondroitin sulfate proteoglycans (CSPGs) as an auxiliary receptor in the absence of HSPGs[16,17] (Fig. 1). Studies designed to map the chondroitin sulfate

Table 1. Examples of attachment receptors for animal viruses

Family	Virus	Receptor	Reference
Adenoviridae	Adenovirus	CAR	53
		HSPGs	32
		sialic acid	128
Bunyaviridae	Hantavirus	β_3 integrins	129
Caliciviridae	Norovirus	HSPGs	130
Circoviridae	Circovirus	CSPGs	131
		HSPGs	
Filoviridae	Ebola virus	DC-SIGN	93
Flaviviridae	Dengue virus	DC-SIGN	88
		HSPGs	132
	HCV	DC-SIGN	90
		HSPGs	1
		SR-B1	97
Herpesviridae	CMV	HSPGs	133
		DC-SIGN	92
	HSV1 and 2	HSPGs	8
		CSPGs	18
	KSV (HHV8)	DC-SIGN	77
		HSPGs	76
		$\alpha_3\beta_1$, $\alpha_2\beta_1$	75
	HHV7	CD4	134
Orthomyxoviridae	Influenza A virus	α2,3 sialic acid (avian)	104
		α2,6 sialic acid (human)	96
		mannose receptor	
Paramyxoviridae	RSV	HSPGs	135
	Sendai virus	α2,3 sialic acid	136, 137
Picornaviridae	Coxsackie	CAR	53
		$\alpha_v\beta_3$	138
	Rhinovirus	ICAM-1 (CD54)	50
	Rhinovirus 87	sialic acid	139
	Rhinovirus 89	HSPGs	3
	FMDV	HSPGs	140
		$\alpha_v\beta_3$	141
	Echovirus	$\alpha_2\beta_1$, $\alpha_v\beta_3$	57 142
Poxviridae	Vaccinia virus	HSPG	143
		CSPG	144
Retroviridae	HIV	CD4	145
		HSPGs	6
		DC-SIGN	94
		Langerin	82
		mannose receptor	
	HTLV	DC-SIGN	146
		HSPGs	25
Reoviridae	Rotavirus	α2,6 or α2,3 sialic acid*	110
		$\alpha_2\beta_1$, α_4	61, 65
Rhabdoviridae	Rabies virus	NCAM	147

*Animal strains of rotavirus use terminal sialic acid for attachment to target cells but evidence to date suggests that human strains do not.

binding domains have shown that there is some redundancy between CSPG and HSPG attachment with the binding sites mostly overlapping, although subtle differences are apparent.[18] In addition to HSV, CSPGs can support the binding of other viruses to target cells (Table 1) and it is likely that many viruses that associate with HSPGs may also interact with chondroitin sulfate containing GAGs.

HIV

HIV-1 binds HSPGs via its surface envelope glycoprotein, gp120. The surfaces on gp120 mediating this interaction have been partially defined, and appear to consist of two structures: the V3 loop and the CD4-induced (CD4i) surface. These two regions form the chemokine receptor binding surface, and contain patches of positively charged amino acids that contribute to HSPG binding (Fig. 2). The ability of HIV to interact with HSPGs depends on several factors, and is linked to the tropism of the virus. The dominant determinant of HSPG binding is the charge on the V3 loop, and this appears to be linked to whether the virus uses CXCR4 or CCR5 as its entry coreceptor. CXCR4-using (X4) viruses tend

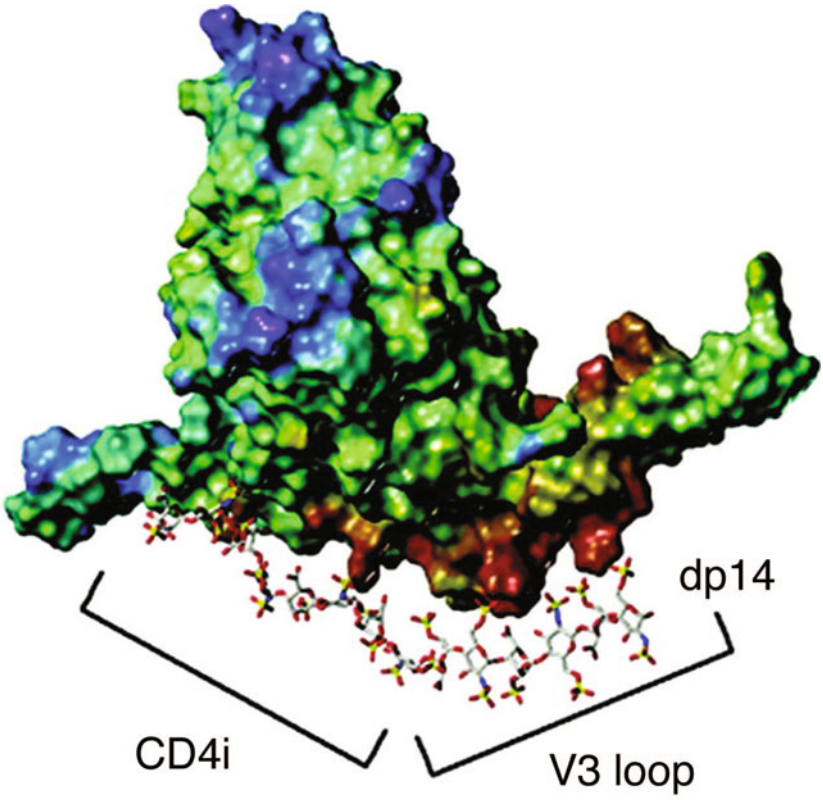

Figure 2. Model of HIV gp120 surface complexed to heparin (14 repeating disaccharide units) is shown with the CD4-induced and the V3 loop indicated. The surface of gp120 is color-coded according to electrostatic potential from blue (most negative) to red (most positive). Reprinted from Vives RR et al. J Biol Chem 2005; 280(22):21353-21357.[20]

to have a more basic V3 loop, and associate more tightly with HSPGs than CCR5-using (R5) viruses.[19] Moreover, the charge on the V3 loop is most likely increased during viral passage in HSPG-rich cell types such as human T-cell leukaemia virus (HTLV)-transformed T-cell lines. Thus, selection pressure on the virus to attach efficiently to HSPG-containing cell surfaces drives gp120 adaptation to a more positively charged surface. This selection, amongst others, results in viruses termed T-cell line adapted (TCLA). The charge on the V3 loop of TCLA viruses may reach +9, whereas that on an R5 primary isolate (PI) that has never been passaged in cell lines is typically +2 to +5. The affinity of monomeric X4 gp120 interaction with the prototype GAG heparin has been measured at 200nM in the absence of sCD4, and 17nM in the presence,[20] confirming the two site binding of gp120 to GAGs. Semi-quantitative analysis of X4 HIV virion binding to $HSPG^+$ cells (HeLa) demonstrates that, as expected, the overall avidity of the interaction is much higher than that for monomeric gp120, no doubt as a result of multivalent gp120-HSPG interactions.[6] Although there is a wealth of information regarding TCLA virus-HSPG association in vitro, little information is available regarding the importance of HSPGs in primary isolate HIV-1 attachment.[21] Moreover, very little is known concerning the use of HSPGs by HIV-1 on primary cells. Recently it has been observed that primary $CD4^+$ T cells express low levels of HSPGs under certain conditions,[2] although we have no insight into whether this makes these cells better targets for HIV-1 infection. There is evidence (our unpublished results) that CD4 is the dominant attachment receptor for TCLA virus on $CD4^+$ T cells, suggesting that other factors such as HSPGs may play a more minor (if any) role. However, it should be noted that primary isolates of HIV-1 tend to have a much lower affinity for CD4 than TCLA viruses[22,23] and so under these circumstances HSPGs may play a more significant role. Macrophages express the proteoglycan syndecan-II upon maturation, facilitating HIV-1 attachment to, and infection of, these cells.[4] It will be of interest to see whether the same is true of dendritic cells and other related cell types. Finally, nothing is known regarding the relationship between HIV-1 and HSPGs in vivo. One can speculate that HSPGs may promote HIV-1 infection in vivo by facilitating virus adsorption to target cell membranes, assuming that sufficient HSPG is expressed, that the viral V3 loop is sufficiently basic, and that the CD4i region is at least partially constitutively exposed. A recent study suggested that HSPGs might allow HIV-1 to be taken up into a protected intracellular environment and subsequently represented to permissive target cells.[5] However, it seems equally, if not more likely, that HSPGs ubiquitously expressed on epithelial and endothelial cell surfaces would trap HIV-1 onto (or into) a nonpermissive cellular environment that would lead to virus inactivation before viral 'rescue' by infection in trans of a permissive cell type.[22]

In a twist to the established HIV-1-GAG interaction story, it has been noted that HIV-1 can take up proteoglycans during budding from infected cells expressing these molecules at the plasma membrane.[24] The chemokine RANTES, when oligomeric, cross-linked the virions to target cell membranes and thereby enhanced viral infection of those cells. Thus, RANTES may have opposing effects on viral infection of $CD4^+$ cells: inhibition by coreceptor occupation but enhancement by increasing viral attachment.

HTLV-1

The surface Env subunit (gp46) of a related retrovirus, HTLV-1, binds HSPGs in an efficient manner, leading to enhanced HTLV pseudotype infection and HTLV-1 Env-mediated cell-cell fusion.[25] Moreover, even though human T cells express low levels of HSPGs after activation, this may be sufficient to increase infection by HTLV-1.