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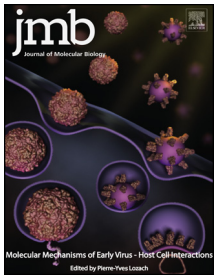

Virus–Receptor Interactions: The Key to Cellular Invasion

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Abstract

Virus–receptor interactions play a key regulatory role in viral host range, tissue tropism, and viral pathogenesis. Viruses utilize elegant strategies to attach to one or multiple receptors, overcome the plasma membrane barrier, enter, and access the necessary host cell machinery. The viral attachment protein can be viewed as the "key" that unlocks host cells by interacting with the "lock"—the receptor—on the cell surface, and these lock-and-key interactions are critical for viruses to successfully invade host cells. Many common themes have emerged in virus–receptor utilization within and across virus families demonstrating that viruses often target particular classes of molecules in order to mediate these events. Common viral receptors include sialylated glycans, cell adhesion molecules such as immunoglobulin superfamily members and integrins, and phosphatidylserine receptors. The redundancy in receptor usage suggests that viruses target particular receptors or "common locks" to take advantage of their cellular function and also suggests evolutionary conservation. Due to the importance of initial virus interactions with host cells in viral pathogenesis and the redundancy in viral receptor usage, exploitation of these strategies would be an attractive target for new antiviral therapeutics.

Introduction

Recognition and interactions with cellular receptors is a critical initial step in the infectious viral life cycle and plays a key regulatory role in host range, tissue tropism, and viral pathogenesis [1]. Viruses are obligate intracellular pathogens that rely on host cell machinery in order to carry out an infectious life cycle and ultimately spread to new host cells. Thus, viruses utilize elegant strategies to orchestrate attachment to one or multiple receptors to cross the plasma membrane and access the necessary host cell machinery. The viral attachment protein can be viewed as the "key" that unlocks the cells by interacting with the "lock"—the receptor—on the host-cell surface, initiating critical downstream steps in the viral life cycle. Viral receptors function not only as attachment moieties but also as entry factors, coordinators of viral trafficking, and activators of signaling events, and in many cases, viruses utilize multiple receptors to carry out different functions within the virus life cycle [2]. Thus, the virus must first find the lock, then use a specific viral "key" or "keys" to unlock the cell. In some cases, viruses must open numerous locks, much like a doorknob plus a deadbolt lock, in order to invade the cell. The numerous functions of viral receptors all coordinate virus targeting to the correct tissues for infection and crossing cellular barriers, which is necessary for the virus to deliver the genome into the host cell [1]. Identification of new viral receptors and defining the mechanism of virus–receptor interactions is an exciting area of research that has revealed the contributions of virus–receptor interactions to tissue targeting, host cell invasion, and viral disease outcomes. Moreover, viruses are incredible tools for studies of cell biology to better understand cellular processes such as ligand–receptor interactions and endocytosis. Furthermore, defining the detailed molecular interactions of viruses and their receptors has also provided significant insights for the development of new antiviral therapies and vaccine technologies.

Interactions with viral receptors are usually mediated by specific viral attachment proteins expressed

on the surface of the virion [2]. The inherent differences in the shape (icosahedral or helical) and the composition of the viral coats (enveloped or nonenveloped) influence the overall architecture of viral attachment proteins. Attachment proteins of enveloped viruses are generally spike-like and extend from the surface of the virion allowing the attachment protein to serve as the first point of contact with the receptor on the plasma membrane [1]. Nonenveloped viruses can either be spherical in nature without extensions, such as polyomaviruses [3], or be decorated with viral proteins that extend from the virion surface, such as reoviruses [4]. Its seems rather apparent that the spike-like protein would be the first contact point between the virus and host cell, in comparison to a viral capsid protein that is embedded on the surface of a spherical viral capsid. However, although reovirus has a spike-like protein that engages cellular receptors, there are additional receptor interactions mediated by capsid components [5, 6]. In addition, while the overall shape of particles can influence attachment protein architecture and the mechanisms by which virions engage cellular receptors, virus–receptor interactions have also been successfully modeled by pseudo-coating viral particles with glycoproteins from an unrelated virus. Pseudotyping viral particles has proved to be a powerful tool for functional analysis of virus–receptor interactions, tissue tropism, and immunity especially for human immunodeficiency viruses (HIV) and highly pathogenic viruses such as Ebola virus (EBOV) [7–10]. Effectively pseudotyping virions that recapitulate patterns of infectious native virions suggests that attachment protein architecture and stoichiometry of attachment protein-receptors is not always essential for viruses to locate and activate the appropriate receptors for infection.

Novel and traditional techniques have both proved to be extremely useful in the discovery of viral receptors. Detailed cellular and molecular studies have revealed the mechanisms by which virus receptors function to mediate attachment, entry, and signaling events [1, 2]. Enveloped viruses can directly fuse with the plasma membrane or fuse with endosomal membranes following endocytosis, while nonenveloped viruses usurp the function of cellular receptors to mediate viral entry events. Despite the mechanism of entry, the initial interactions with viral receptors usually prime the cell for viral invasion [1]. Biochemical and structural analyses have provided a great deal of insight into the molecular interactions between viruses and receptors [4, 11, 12]. Atomic-level resolution has revealed not only the functionality of virus–receptor interactions but also the conservation in these interactions among viruses, providing new insights into viral evolution as well as a better understanding of ligand–receptor interactions [11, 13–15]. Detailed molecular information on virus–receptor interactions also serves as a platform for the development of novel anti-viral strategies, which can be applied broadly to the field of virology as well as receptor biology.

Initial interactions between viruses and receptors are varied and can range from nonspecific to highly specific. In many cases, viruses first engage a receptor in a low-affinity, high-avidity interaction and then have a subsequent interaction with a secondary or tertiary receptor in a high-affinity interaction event [16, 17]. The initial low-affinity interactions can occur through electrostatic (van der Waals) interactions, yet the low-affinity nature of these initial events does not imply a lack of specificity [18]. In fact, the initial interaction with the host cell is highly regulated regardless of the whether it is a low or high-affinity binding event as receptor interactions are a key regulatory step in viral tissue tropism and infection. In general, viral interactions with high-affinity receptors usually take place with a more specialized receptor after low-affinity binding events [5, 17, 19]. Virus–receptor interactions can mediate conformational changes in the viral attachment proteins, function in entry, or activate signaling pathways that are necessary for the infectious life cycle of the virus [1]. The initial low-affinity interactions of many viruses with host cells occur through interactions with carbohydrates such as sialylated glycans or sialic acids (SAs) [18]. Furthermore, the majority of cellular receptors identified for viruses can be organized into the category of cellular adhesion molecules (CAMs) [5, 20–22] and more recently the phosphatidylserine (PtdSer) family of receptors [23–25] (Fig. 1). The commonalities in viral receptor usage suggest that viruses utilize “master locks” in order to mediate cellular attachment, entry, and signaling events (Fig. 2). The redundancy and conservation of this initial binding event offers elegant parallels in its simplicity on the surface, yet is a site of complicated forces that dictate disease outcomes by regulating viral tropism, spread, pathogenesis, and host jump. Given the vast array of literature and the importance of this topic, this review is divided into common themes that demonstrate the elegance of redundancy and conservation in virus–receptor interactions.

Master locks: virus interactions with SA receptors

A wide range of viruses have been shown to utilize SA receptors to mediate the initial attachment to the host cell surface. In some cases, these interactions orchestrate additional steps in the virus life cycle, such as virus internalization or activation of signaling events [12, 26]. SAs are derivatives of neuraminic acid, which is a monosaccharide with a nine-carbon backbone that terminate glycan chains of asparagine (N-) or serine/threonine (O-)linked glycoproteins and glycolipids and have net negative charge [27–29]. SA structures are highly diverse, with over 50 different SA structures found in nature due to the

potential for many modifications through acetylation or methylation of the hydroxyl groups [30]. The most commonly found SA in humans is the 5-*N*-acetyl neuraminic acid (Neu5Ac) in which the 5-carbon position is modified with an N-acetyl group [27]. SAs are further diversified through different α linkages from the 2-carbon position to the main sugar chain of the glycoprotein or glycolipid. The most common linkages are α2,3- or α2,6-linked to the Gal or GalNAc residue commonly referred to as α2,3 or α2,6-linked SA. SAs can also attach to other internal Sia residue resulting in an α2,8-linked SA [27]. Gangliosides are SA-containing glycosphingolipids that consist of an extracellular oligosaccharide with one or more SA and a ceramide chain that is embedded in the plasma membrane. Due to high level of heterogeneity and diversity, over 188 gangliosides have been identified in vertebrate tissues to date [31]. Based on this complexity, gangliosides are organized into groups based on the complexity of their SA branching patterns, and referred to as mono-, di-, tri-, and tetra-sialogangliosides or asialo, a, b, or c "series" gangliosides [32]. Sialylated glycans are ubiquitously expressed on the surface of host cells and function in many important biological processes including development, cell adhesion, and signal pathways in lipid-rich microdomains such as caveolae [27, 31]. Glycans such as gangliosides are so crucial to normal cellular processes, that alterations in ganglioside expression or function can result in disease states such the lysosomal storage disease, Tay–Sachs disease, Guillain–Barré syndrome, infantile-onset epileptic syndrome, and Alzheimer's disease [31, 33, 34]. The ubiquitous expression, diversity, and positioning of the branched SA structures on the surface of eukaryotic cells make them an attractive target for pathogen attachment to host cells.

Virus–SA interactions may therefore serve as a first point of cell contact, which leads to additional interactions with secondary proteinaceous receptors that mediate entry, or SA may be the sole receptor that is capable of inducing conformational changes and subsequent fusion events [1, 26]. The common usage of SA receptors extends across viral genome types and viral families including the enveloped coronaviruses (+ssRNA) [35] and influenza viruses (−ssRNA) [36], and the nonenveloped reoviruses (dsRNA) [18] and polyomaviruses (dsDNA) [12], which are discussed herein. Moreover, SA expression can be a key determinant of tissue tropism and can have a major impact on viral disease outcomes, leading to strain-specific and cell-type dependent differences in viral pathogenesis [37, 38]. Furthermore, SA-binding sites are oftentimes a target of neutralizing antibodies and are an emerging target for antivirals [39–42]. Recent advances include the use of glycan array screening to better define virus–glycan interactions [43, 44]. Glycan arrays are high-throughput screens in which purified viral proteins expressed as recombinant proteins or on nanoparticles are analyzed for binding to a wide distribution (up to 500) of synthetic glycans that have been robotically printed on a glass slide [45, 46]. Glycan array screens have been employed for many virus–glycan studies and deposited into the Consortium for Functional Glycomics including over 500 glycan array studies specific for influenza virus [47, 48]. Combinatorial approaches of glycan array screening together with structural–functional analyses have shed new insights into the utilization of SA receptors for a number of viruses including several important pathogens including influenza A virus (IAV) [48], Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV) [35], and polyomaviruses [3, 12, 38] discussed in more detail below.

Influenza A virus

IAV, a member of the *Orthomyxoviridae,* is a prototype example of a virus that utilizes SA to mediate host cell invasion, and SA expression within the host regulates tissue tropism and host range specificity [36, 37]. IAV is a segmented single-stranded RNA (−ssRNA) virus encased in a lipid envelope with glycoproteins hemagglutinin (HA) and neuraminidase (NA) that extend away from the surface of the virion envelope [49]. HA confers binding to SA receptors, while NA is necessary for viral release from sialyl linkages on host cells during viral budding [50]. Following SA binding, IAV enters cells by receptor-dependent endocytosis [51] or marcopinocytosis [52] and HA mediates fusion of the viral membrane with endosomal membranes [53]. It has recently become clear that binding to SA receptors alone is not sufficient to mediate entry, and rather IAV entry is facilitated by C-type lectin receptors (CLRs), dendritic cell-specific intercellular adhesion molecular 3-grabbing non-integrin (DC-SIGN or CD209), and L-SIGN (CD209L) [51]. The complexity in understanding the HA-SA interactions is complicated by the mere number of hosts that are susceptible to IAV including humans, bats, and avian and swine species [37, 54, 55]. There is further complexity in variation due to at least 18 HA and 11 NA subtypes and the potential for viral gene segment mixing due to reassortment [37]. Like many other viral attachment proteins, HA and NA are antigenic sites subject to host immune pressures that can be neutralized by antibodies [56]. IAV high mutation rates allows for amino acid changes in HA, which can result in host immune evasion, but also results in antigenic drift, while reassortment of viral gene segments in a reassortment reservoir can result in antigenic shift [57]. Reassortment and antigenic drift are responsible for the widespread epidemics and pandemics that arise due to host immune evasion [54].

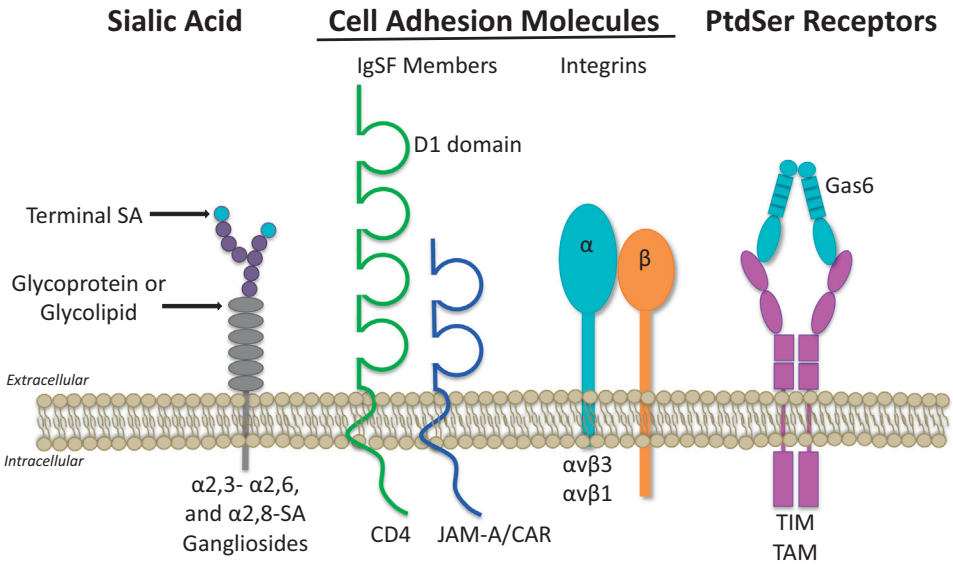

Fig. 1. Classes of common viral receptors. Common viral receptors include sialylated glycans such as SAs and SA-containing gangliosides, CAMs such as igSF members including CD4, JAM-A, CAR and integrins such as αvβ3, and PtdSer receptors, cell immunoglobulin and mucin domain (TIM), and the Tyro3, Axl, and Mer (TAM) receptors. Virus binding to IgSF members is mediated through the D1 domain.

IAV has a broad host range in nature including humans [57]. IAV is responsible for annual seasonal flu epidemics and for the most severe influenza pandemics including the 1918 H1N1 pandemic and the more recent 2009 H1N1 pandemic [57]. The pandemic potential has been highlighted recently with H7N9 avian influenza virus that can infect humans and cause severe respiratory disease, as it is assessed to have the greatest pandemic potential if the virus gains the ability to spread person-to-person [37, 58, 59]. Epidemics and pandemics result from the emergence of new influenza strains into a naïve human population, which has not been exposed to the antigenically distinct strain derived from a different host, and thus lacks pre-existing immunity [60]. The main factor that leads to host jump are changes in the receptor-binding properties of the viral HA, which is a key antigenic determinant

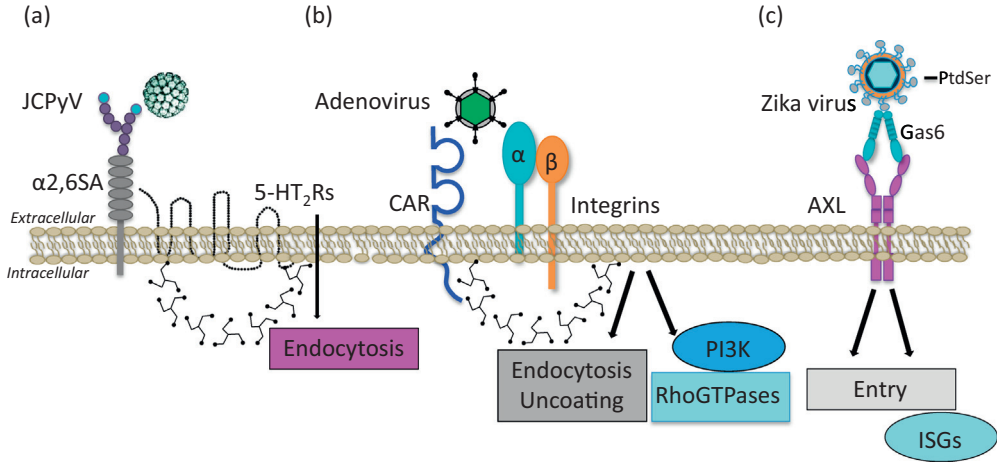

Fig. 2. Viral receptors function to unlock host cells. (a) JCPyV attaches to host cell α2,6 SA-containing LSTc and requires 5-HT_2 receptors for internalization, presumably through clathrin-mediated endocytosis (CME). (b) Adenovirus binds to CAR then binds to integrins including αvβ3 and αvβ5 to mediate CME, activation of signaling events through PI3K, and activation of Rho GTPases to induce actin remodeling. (c) Zika virus utilizes the AXL receptor tyrosine kinase (AXL) through AXL ligand Gas6, which bridges AXL and PtdSer on the viral envelope to mediate viral entry and activation of the Type 1 IFN pathway and IFN-stimulated genes (ISGs).

[37]. Thus, gaining a better understanding of the interactions of influenza virus with host cell receptors in addition to understanding the receptor expression within the broad range of hosts that IAV infects is paramount in our future understanding of IAV pathogenesis and disease control.

The HA of IAV binds to terminal α2,3 and α2,6 SA residues linked to a galactose (SA α2,3-Gal or SA α2,6-Gal) on glycoproteins and glycolipids [18, 37, 48]. In humans, α2,6-linked SA is predominantly expressed in the upper respiratory tract, while the α2,3-linked SA are mostly expressed in the lower respiratory tract [61]. Human influenza viruses, or influenza viruses with HA derived from a human strain, usually bind to α2,6-linked SA in the upper respiratory tract, while those of avian species generally bind to α2,3-linked SA in the lower respiratory tract [37, 62]. Thus, in some cases, avian species have been able to infect humans when the virus is capable of infecting cells in the lower respiratory tract [37], presumably through a deep inhalation, resulting in a host jump. In most cases of interspecies transmission, changes in receptor-binding properties have led to a host jump. One such change can result from reassortment of viral gene segments that can occur in reservoir hosts that express both α2,3- and α2,6-linked SA receptors including swine and avian species such as chickens and ducks contributing to evolution of IAV. For example, swine express both α2,3- and α2,6-linked SA in the respiratory tract, and thus are susceptible to IAV strains that utilize both types of SA receptors and serve as a mixing vessel for reassortment of viral gene segments leading to the generation of novel IAV strains [36, 37, 63]. Most avian species express abundant levels of α2,3-linked SA in the upper and lower respiratory tracts and intestinal tract, while there is varied expression of α2,6-linked SA in these tissues. For example, in the majority of ducks and geese, there are low levels of α2,6-linked SA in the upper respiratory tract yet abundant expression of these receptors in the lower respiratory tract and the large intestine [64]. Changes in the SA binding properties that arise within HA due to a high mutation rate can change the SA binding preferences, thus resulting in host jump (reviewed in Ref. [37]). Mutations in HA have been identified by sequencing influenza virus isolates and further analyzed experimentally for SA binding through various techniques including glycan arrays, which has proved useful for high-throughput screening of pathogenic influenza strain HA-binding properties [65–67]. For example, analysis of the 2009 H1N1 pandemic IAV revealed that it was capable of binding to both α2,3- and α2,6-linked SA [48]. Moreover, recent studies suggest that new world bats harbor novel influenza strains and little brown bats have been shown to have both avian α2,3- and human α2,6-linked SA receptors, suggesting that bats could also be an IAV reservoir and could lead to the emergence and spread of new IAV strains [68, 69]. Bats are reservoirs for a number of zoonotic RNA viruses including the filovirus EBOV and severe acute respiratory syndrome (SARS)-related coronaviruses, and thus their implication as an IAV reservoir deserves serious attention due to their abundance and ability to spread virus [70–72]. Taken together, alterations in SA preference and diversity with respect to binding properties can influence host range and can also lead to the emergence of pandemic strains of influenza virus.

HA is a type 1 integral membrane glycoprotein that is post-translationally modified by glycosylation of the N-terminus and acetylation of the cytoplasmic domain [36, 50]. The mature form of HA is a homotrimeric protein that extends from the virion envelope and comprises three monomers of the membrane-distal globular head domain (HA1) and membrane-proximal stem domain (HA2) [53]. The HA0 precursor is cleaved by cellular proteases into HA1 and HA2 either on the cell surface or in trans-Golgi network [73]. This initial proteolytic activation is required for HA maturation [53], providing an extra layer of security over the "key" to influenza infection. HA1 contains the receptor-binding domain (RBD), while HA2 domain mediates fusion of the viral and host membranes following endocytosis [53]. The RBD within the globular head is a pocket surrounded by three structural elements that rim the pocket with a base formed by highly conserved residues [37], which can be viewed as the knob and spindle of a lock assembly, respectively. Analysis of HA interactions with SA receptors has been performed by soaking HA with linear sialylated α2,6-linked lactoseries tetrasaccharide c (LSTc) pentasaccharide or α2,3-linked LSTa SA as cognate reference receptors [36]. The rim of the RBD is formed by the 130-loop, 190-helix, and 220-loop (numbering based on H3 HA) [18, 37]. Hydrogen bonds connect the side chains in the 130-loop with SA, while additional glycan interactions occur with the 190-helix and the 220-loop [18, 37, 74]. The base of the RBD is formed by the highly conserved residues Y98, W153, H183, and Y195, which stabilize binding to SA receptors through van der Waals interactions [37]. SA interactions within the RBD are conserved among influenza viruses [37].

The conserved regions within the RBD lend specificity to binding of SA receptors owing to species specificity, and mutations within these sites result in enhanced interspecies transmissibility and host jump. Interestingly, H1N1 strains that have adapted to infect humans and caused the 1918 (Spanish flu) and 2009 (Swine flu) influenza pandemics have specific HA mutations that enhance binding for the human α2,6-linked SA receptor. Avian isolates with resides E190 and G225 in the RBD are capable of binding to both α2,3- and α2,6-linked SA, while human-adapted isolates with

mutations in E190D and G225D/E have enhanced specificity for the human α2,6-linked SA receptor and combinatorial mutations result in dual receptor specificity [37, 75, 76]. Influenza strains bearing H5 HA such as avian H5N1 have caused human infections from avian transmission but are not transmitted human-to-human presumably because H5 HA does not exhibit preference for the human α2,6-linked SA receptor [37, 77]. However, experimentally modified H5 HA through site-directed mutagenesis and serially passage in ferrets or reassortment of H5 with H1N1 lead to preference for the human α2,6-linked SA receptor through multiple mutations in HA [78, 79]. Most notably, a common mutation, Q226L, was identified in the H5 HA from two different strains, and this particular mutation results in an increased hydrophobic environment, and other mutations result in deletion of a glycosylation site near the RBD leading to increased binding to α2,6SA [37, 78, 80]. Interestingly, mutations in Q266 have arisen in H2, H3, and H7 subtypes as well [81, 82]. H7N9 has low prevalence in humans, yet after infections occurred in China in 2013, it has been predicted to be the next potential cause for an influenza pandemic due to the severity of disease in humans [59]. The Anhui-H7N9 strain is the most common in humans and has the capability of binding to both avian α2,3 and human α2,6-SA receptors. This strain contains mutations in the RBD including Q226L as well as surrounding mutations including G186 V leading to increased binding to α2,6-SA receptors [37, 82]. Taken together, these data show that minor amino acid substitutions in conserved regions of the RBD of HA confer enhanced affinity and specificity for the human α2,6-SA receptor [37]. In addition to specific amino acid substitutions, a comparative large-scale analysis of glycan array data revealed that host-specific substructures that affect the glycan chain angles can also distinguish glycan binding and host tropism [48]. Thus, modifications to RBDs can therefore lead to species jump and also increase the likelihood for transmission to humans and potential influenza pandemics.

Middle East respiratory syndrome coronavirus

The MERS coronavirus (MERS-CoV) is a clade C betacoronavirus that recently emerged on the Arabian Peninsula from the dromedary camel reservoir gaining the ability to infect humans, causing >2000 lower respiratory tract infections and 750 related deaths to date [83] with clinical features similar to SARS-CoV [84, 85]. MERS-CoV is an enveloped, +ssRNA virus that expresses the transmembrane spike (S) glycoprotein that extends on the surface of the viral envelope. MERS-CoV binds to SA through interactions with the viral spike protein, and has demonstrated preference for α2,3-linked SA over α2,6-linked SA, to mediate viral attachment [86]. Interestingly, the preferential binding to α2,3-linked SA correlates with the expression of α2,3-linked SA in the lower respiratory tract, the site of MERS-CoV replication [35]. Thus, the expression of the α2,3 linked SA is a key determinant of tissue tropism and is also of great zoonotic potential for host jump from animals such as the dromedary camel reservoir to humans [35, 87].

The viral spike (S) protein is a metastable prefusion homotrimer, comprising two subunits, the N-terminal S1 and C-terminal S2 subunit [35]. The S1 subunit contains the receptor binding domains, an N-terminal domain and a C-domain, while the S2 subunit contains the fusion domain [88–90]. A recent cyroEM structure determination of the MHV S1 revealed that the subunit is divided into four subdomains with distinct receptor-binding properties $S1^A$–$S1^D$ [90, 91]. The $S1^A$ and $S1^B$ subdomains are reported to function in both proteinaceous and SA-receptor binding for betacoronaviruses [92–94]. For most reported coronaviruses, the spike protein $S1^A$ subdomain is a SA binding domain, and the $S1^B$ subdomain is the binding site for the proteinaceous receptors such as dipeptidyl peptidase 4 (DPP4) for MERS-CoV [89, 95–97]. Crystal structure analysis of MERS-CoV S1 revealed that a receptor-binding subdomain within the RBD mediates interactions with the viral entry receptor DPP4 [95–97]. The recent finding that MERS-CoV binds to SA in addition to the DPP4 receptor suggests that SA binding could play a regulatory role in host jump, tissue tropism, and pathogenesis of MERS-CoV [35, 98]. Other viral attachment proteins have also been demonstrated to bind to both a sialyl-containing glycan as well as a proteinaceous receptor such as mammalian reovirus [18, 99, 100]. For example, the σ1 attachment protein that extends away from the surface of the viral capsid of the nonenveloped, dsRNA reovirus contains binding sites for sialylated glycans [18, 100, 101] as well as junctional adhesion molecule A (JAM-A) [99]. Thus, new information suggests that MERS-CoV requires SA receptors in addition to the proteinaceous DPP4 receptor through distinct binding sites in the $S1^A$ subdomain, and SA binding of MERS-CoV likely has important implications in host range and transmission [35].

The utilization of a SA receptor is not unique among coronaviruses, as other beta-CoVs utilize SA-containing receptors to mediate entry [102–105], while other CoVs bind to SA to mediate viral attachment and utilize a separate entry receptor [89, 106, 107]. However, the strategy utilized to define the MERS-CoV-SA interaction was an elegant example of creative molecular biology and biochemistry. Li *et al.* [35] utilized a *Lumazine synthase* protein of *Aquifex aeolicus* bacterium that was able to self assemble into an icosahedral nanoparticle, which was then used as the core for expression of Fc-tagged MERS-CoV S1

protein S1^{A} domain. The nanoparticles were then utilized for functional studies and for glycan array screening, through which α2,3-linked SAs were found to be the preferred sialoglycans [35]. Sialoglycan receptors serve to mediate MERS-CoV attachment specifically, and removal of SA results in significantly reduced infection in human airway epithelial cells. In addition, expression of α2,3-linked sialoglycans correlates with sites of MERS-CoV replication including the nasal epithelium of dromedary camels and alveoli of human lung [35]. Purification and expression of viral attachment proteins thus allows for specified study of direct interactions of presumed low-affinity binding events. Further fine-tuning can be employed to define the precise interactions biochemically, which can then be confirmed through additional functional studies. This important finding that MERS-CoV engages a SA receptor in addition to DPP4 [35] provides a broader understanding of the host cell factors required for host cell invasion and highlights new information regarding cell surface structures shared among coronavirus host species that could enable host jump and infection.

Polyomaviruses

Polyomaviruses are nonenveloped, dsDNA viruses that generally have a narrow host range in nature yet can cause a range of disease outcomes in their natural hosts including asymptomatic infections, skin cancer, and a fatal central nervous system (CNS) disease [108]. BK polyomavirus (BKPyV) infects the renourinary tract and establishes a persistent infection in healthy individuals yet causes polyomavirus associated nephropathy and polyomavirus-associated hemorrhagic cystitis during immunosuppressed conditions such as transplantation [109]. JC polyomavirus (JCPyV) causes an asymptomatic, lifelong persistent infection in the kidneys of healthy individuals but can cause the fatal, demyelinating disease progressive multifocal leukoencephalopathy (PML) in the CNS of immunosuppressed patients [110]. Simian virus 40 (SV40) and mouse polyomavirus (PyV) are well-studied model virus systems, and PyV has been used for pathogenesis studies in the mouse model. Studies of human polyomaviruses have gained recent traction due to the rapid identification of human polyomaviruses in the past decade with particular interest in Merkel Cell polyomavirus, which causes Merkel cell carcinoma, a rare but aggressive skin cancer [111]. Understanding the interactions between polyomaviruses and their cell surface receptors will provide insight into the limited tissue tropism and host range of polyomaviruses that actually cause a wide range of diseases.

The majority of the polyomaviruses studied to date have been confirmed to use SA receptors to mediate either binding to the host cell surface and/or entry [15]. Viral protein 1 (VP1) is a surface-exposed pentameric protein that makes up the viral icosahedral capsid through the interconnectivity of 72 VP1 pentamers [112] and is the viral attachment protein for all known polyomaviruses [113, 114]. Each monomer of VP1 forms the antiparallel beta sandwich fold that is commonly represented in viral capsid proteins [15]. The antiparallel beta strands are linked by loops that connect the beta strands B,I,D,G and C,H,E,F [3, 38]. While all polyomaviruses have been demonstrated to utilize SA receptors, the nature of these interactions is unique, yet for SV40, BKPyV, and JCPyV, there are common themes and conserved mechanisms that extend across these polyomaviruses [3, 38, 115]. The majority of studies to further elucidate polyomavirus interactions with SA receptors have been conducted through the use of glycan array screens utilizing purified VP1 pentamers and accompanying structural–functional studies [3, 38, 115].

SV40, BKPyV, and PyV all utilize ganglioside receptors containing α2,3- and α2,8-linked SA to mediate viral attachment to respective host cells [3, 38, 115–117]. SV40 polyomavirus utilizes the α2,3-linked ganglioside GM1 [115, 118], while the α2,8-disialic acid containing b-series gangliosides GD3, GD2, GD1b, and GT1b can all enhance BKPyV infection [3]. The common α2,8-disialic acid motif in the b-series gangliosides is the preferred binding epitope for BKPyV, which explains why multiple ganglioside types within the series can support BKPyV infection [3]. Interestingly, comparison of the X-ray crystal structures of BKPyV in complex with GD3, and SV40PyV in complex GM1 revealed extensive conservation in the RBD. However, a major difference in receptor interactions was determined by a single residue, Lys68 in BKPyV and Ser68 in SV40 [3, 115]. In the case of BKPyV, the Lys68 is positioned such that it blocks the potential binding of GM1, although many of other potential GM1-interaction sites are conserved. Interestingly, experimental mutation of the Lys in BKPyV to a Ser expressed in SV40PyV conferred binding of BKPyV to the SV40 receptor GM1 and infection in GM1-expressing cells [3]. The ability to switch the receptor usage of BKPyV, which predominantly infects the kidneys in human hosts, to receptor for the SV40, suggests a strong sequence and structural conservation in VP1s of polyomaviruses from different species [3, 15, 115]. Furthermore, the ability to induce a “receptor switch” through a single point mutation illuminates the likelihood that BKPyV is an evolutionary descendent of SV40 that underwent a selective pressure to utilize the b-series ganglioside receptors within the host. One such possibility could be due to the availability and expression of the ganglioside receptors in specific host tissues, highlighting again that receptor expression and specificity are a major determinant of tissue tropism and viral pathogenesis.

In contrast to SV40 and BKPyV, JCPyV has been suggested to utilize either α2,3-linked or α2,6-linked SA [38, 119–124]. However, a glycan array screen with purified VP1 pentamers of the JCPyV-1a strain Mad-1, a strain isolated from the brain of a PML patient, revealed that JCPyV binds specifically to α2,6-containing SA receptor motif LSTc [38]. Interestingly, Mad-1 VP1 pentamers only bound to LSTc and not to any other glycans in the screen including α2,3-linked and α2,6-linked SA-containing receptors such as gangliosides [38]. LSTc was confirmed as a specific receptor motif through X-ray crystal structure of JCPyV VP1 in complex with LSTc and functional assays. The co-crystal structure of VP1 and LSTc demonstrated that the LSTc binding site is formed by the BC-, DE-, and HI-loops of one monomer and the BC-loop from a clockwise neighboring monomer [38]. Specific VP1 residues (L54, N123, S266, and S268, also referred to as L55, N124, S267, and S269 in conventions when counting the Met start codon) are required for VP1 binding to LSTc. The crystal structure revealed extensive interactions with the terminal SA, including parallel hydrogen bonds to the side chains of S266 and S268 and terminal Neu5Ac residue [38]. Interestingly, a comparison of the VP1 structure in complex with LSTc and alone revealed that VP1 undergoes induced fit movements to accommodate LSTc binding. The hydrogen bond between the GlcNAc and N123 also leads to binding organization of LSTc in a kinked "L"-shaped conformation [38].

Comparison of VP1 in complex with SA receptors for JCPyV, BKPyV, and SV40, which share >74% sequence identity, reveals conservation within the SA-binding pocket and the same VP1 loops are involved in binding to each of their SA-containing receptors [3, 15, 115]. Despite the engagement of distinct SA receptors, all three polyomaviruses engage glycans that terminate in Neu5Ac [3, 38, 115]. The specificity of the binding pocket is further defined by a number of additional contacts that line the core of the SA-binding pocket [124]. Interestingly, VP1 pentamers of the JCPyV-1a strain Mad-1 strain did not bind to any other glycans included on the glycan array including any of the SA-containing ganglioside receptors [38]. However, VP1 pentamers or virus-like particles of either the Mad1a strain or the WT3 (a urine isolate) strain have been demonstrated to interact with SA-containing ganglioside receptors including those with α2,3-linked- and branched α2,8-linked SA through other biochemical-based assays [120, 123]. Examination of the VP1 structures of Mad1a and WT3 revealed that the additional contacts that line the core of the SA-binding pocket could possibly influence the engagement of SA binding potential [124]. However, as demonstrated through crystal soaking experiments, VP1 pentamers of both the JCPyV genotype "1a" (brain isolate) and "3" (urine isolate) strains can bind to ganglioside receptors, GM1, GM2, GD1a, and GD1b, albeit only with higher concentrations of the glycans suggesting a significantly reduced affinity [124]. However, functional analysis revealed that gangliosides cannot serve as functional receptors for JCPyV as over-expression of gangliosides does not enhance JCPyV infection and silencing of the GM3 synthase required for ganglioside production did not reduce JCPyV infection [124]. An important theme that emerged from this study is that although JCPyV exhibits binding to α2,3-linked SA, VP1 has a slightly higher affinity for α2,6-linked SA suggesting that affinity is a key determinant in SA receptor usage in addition to receptor recognition and specificity [124]. Overall, these findings highlight that the low-affinity, high-avidity interaction of JCPyV VP1 is highly specific for α2,6-linked LSTc, demonstrating that initial SA-binding events are regulated and thus can play key regulatory roles in tissue tropism and viral pathogenesis.

JCPyV infection during immunosuppression can lead to PML development in HIV-positive individuals and in those receiving immunomodulatory therapies for immune-mediated diseases. In particular, JCPyV-positive individuals receiving natalizumab, a humanized monoclonal antibody (mAb) treatment for multiple sclerosis, that blocks trafficking of autoreactive very late antigen-4+ T- and B-lymphocyte to the brain [125, 126] are at particular risk for PML [127]. In fact, there have been ~756 natalizumab-related cases of PML as of January 2018 [128]. Interestingly, mutations in the exact residues that are critical for LSTc binding and infection of cells (L54, N123, S266, or S268) *in vitro* are found to arise in individuals with PML. In fact, at least one or more mutations in these VP1 residue are found in >90% of the CSF viral isolates from individuals with PML, suggesting that these mutations may be responsible for JCPyV spread and subsequent invasion of the CNS to cause PML [123, 129–131]. Mutations within these residues lead to loss of LSTc binding and loss of infectivity in a number of cell types [132]. However, it is currently unclear whether there are strain-specific differences that could contribute to cell-type permissivity and susceptibility of infection by these PML-mutant viruses or whether PML-mutant viruses can infect cells in a SA or LSTc-independent manner [133–135]. However, the correlation between mutation of key SA-binding residues in VP1 and the development of PML clearly suggests that mutations in VP1 could represent immune escape variants, and thus, VP1 is an attractive target for antivirals. In fact, studies have revealed that VP1-specific antibodies from PML patients cannot neutralize VP1 with PML-associated mutations unless subsequent steps in immune reconstitution are taken as well [40, 134]. These recent findings provide an enhanced understanding of JCPyV infection and PML development and suggest that a major area of novel PML therapeutics should focus on humanized mAbs that target PML-

associated mutations, vaccines that provide VP1-specific immunity and protect from PML-associated mutation infections, in combination with treatments to boost the host immune system [40, 41, 136].

The majority of polyomaviruses have been demonstrated to use SA receptors, and for the most part, polyomaviruses specifically engage ganglioside receptors anchored in lipids on the surface of host cells [32]. The polyomaviruses reported to utilize gangliosides as functional receptors also have been shown to enter cells through non-clathrin-dependent pathways. BKPyV and PyV have been reported to enter cells via a caveolae-dependent pathway [137, 138], while PyV and SV40PyV enter cells through clathrin-, and caveolae-independent, cholesterol-dependent entry processes [139–141]. Non-clathrin endocytic processes are activated upon binding to lipid-linked receptor moieties, and thus, the conservation in ganglioside usage is likely to extend beyond the initial cellular attachment to the functionality of the receptor to mediate endocytic events necessary for viral infection. SV40 interactions with ganglioside GM1 lead to membrane curvature and endocytosis [142] and cellular vacuolization [143]. In addition, binding of PyV to SA-containing gangliosides GD1a and GT1a and α4 integrins leads to activation of the phosphatidylinositol 3-kinase (PI3K) pathway, and PI3K activity is required for PyV endocytosis [144]. Interestingly, JCPyV exhibits low-affinity binding to gangliosides, but does not utilize them as functional receptor, preferring the α2,6-linked SA receptor LSTc specifically as an attachment receptor [38]. JCPyV also requires the proteinaceous receptor, 5-hydroxytryptamine $(5\text{-HT})_2$ receptors, to mediate viral entry [145]. Furthermore, JCPyV is the only polyomavirus shown to date that utilizes clathrin-dependent endocytosis [145, 146] suggesting that engagement of a secondary receptor allows JCPyV to enter in a manner that is unique among polyomaviruses, yet this process has not been fully characterized. Thus, despite the high degree of structural and functional similarities in SA-binding among JCPyV, BKPyV, and SV40, the entry strategies are not conserved and may highlight an evolutionary divergence of JCPyV to engage entry receptors to mediate clathrin-mediated endocytosis that perhaps affects later stages in the infectious viral cycle specific to JCPyV.

Master locks: non-SA viral receptors

Many viruses engage one or multiple specific receptors in order to carry out attachment, entry, and/or signaling [1]. A single virus receptor can carry out one or more of the aforementioned functions or viruses can utilize distinct receptors to mediate each function, thereby lending even greater specificity in tissue tropism. In other cases, a coordination of viral–receptor interactions is necessary to mediate specific functions such as activation of signaling events [1, 144, 147]. Interactions with multiple receptors also provide an extra layer of security to ensure that the virus is targeting an appropriate target cell for infection such as a door having a deadbolt in addition to the doorknob lock. Studies of viral receptors have revealed unique receptors but mostly common receptors that can be categorized as CAMs including integrins, selectins, cadherins, and immunoglobulin superfamily (IgSF) receptors [22]. Recently, PtdSer receptors have been identified as receptors for a range of enveloped viruses [25]. The redundancy in viral receptor usage thus reveals potential evolutionary conservation and suggests that viruses have evolved to utilize particular receptors that convey necessary steps to drive the infectious process within host cells. Furthermore, this redundancy could serve as the platform for broad-spectrum antiviral therapies to inhibit viral infection from a range of viruses. Discussed below are examples of virus utilization of common viral receptors to drive the infectious cycle.

Master locks: cell adhesion molecule viral receptors

Cell adhesion molecules

The majority of viral receptors identified to date are cell adhesion molecules (CAMs) that function in cell-to-cell and cell-to-extracellular matrix adhesion and thus are essential mediators of cellular processes such as development, maintenance of cellular structure, cell signaling, and maintenance and repair of tissues [22, 148]. The broad family of CAM includes selectins, cadherins, integrins, and IgSF members [148]. The ubiquitous expression and multifactorial function of CAMs in ligand binding, endocytosis, and signaling provides a plethora of possibilities for viruses to engage CAMs. Viruses including HIV [149], measles virus [150], reovirus [19], rhinovirus [151], adenovirus [20], poliovirus [152], and coxsackievirus B (CVB) [147] utilize IgSF members as receptors. In addition, integrins serve as receptors for reovirus [153], rotavirus [154, 155], adenovirus [156, 157], West Nile virus (WNV) [158], human metapneuomovirus (hMPV) [159], foot-and-mouth disease virus (FMDV) [160–164], and herpes simplex virus (HSV) [165], as well as human cytomegalovirus HCMV and human herpesvirus-8 [166–168]. CAMs function to mediate attachment, entry, or signaling or multiple steps that enable viral invasion of the host cell. Interestingly, many of the CAMs are exploited by viruses to sneak their way into tight spaces like the tight junctions [99, 169]. For example, it was recently shown that E-cadherin, a component of the adherens junction, is a receptor for hepatitis C virus, a major cause of chronic liver disease [170]. Discussed below are several examples of viruses that utilize the IgSF members as receptors, demonstrating conservation

of similar mechanisms employed by diverse and similar viruses. Overall, the redundancy in receptor usage indicates an evolutionary selection toward particular receptors, which could include common cellular targets, cell surface expression patterns, receptor functionality, or could even suggest that some viruses could have evolved at a time after receptor-binding properties were established.

Immunoglobulin superfamily receptors

IgSF members have emerged as receptors for a wide range of viruses including enveloped and nonevenveloped viruses with either DNA or RNA genomes, including reovirus, adenovirus, coxsackievirus, rabies virus, measles virus, and HIV [17, 22]. The array of viruses that utilize IgSF members to mediate infection is suggestive of a level of redundancy in the usage of IgSF members among viruses. IgSF receptors are an attractive target for viruses due their abundance and diversity. Interestingly, their localization to tight junctions may limit their accessibility to act as virus receptors, yet a number of viruses utilize IgSFs in tight junctions and exploit their functionality to access host cells [17, 22]. IgSF CAMs are transmembrane proteins comprised of one or more Ig folds, comprising two antiparallel β sheets made up four antiparallel beta strands (B, C, E, F) that make up the common core [17, 22] with additional beta strands (A, C′, C″, D, G) [171]. The β strand connectivity gives rise to unique IgSF domains, referred to as V-set, C-set, or I-set Ig domains based on variable, constant, or intermediate structures, respectively. The vast number of IgSF members that have been demonstrated to serve as viral receptors is remarkable, and some common characteristics identified virus IgSF receptor usage have emerged from elegant biochemical, structural, and biological studies [17, 22]. The current structural and biological data suggest that all viruses that utilize IgSF receptors engage the N-terminal D1 domain, which is the most membrane distal domain of the IgSF receptor [17]. In addition, most viruses bind to IgSF receptors with a V-set IgSF fold and bind to the "tip" of the D1 domain by specifically engaging the CC'FG beta-sheet [17]. The common binding sites in IgSF receptors have been exploited by many viruses to drive diverse functions including serving as viral attachment molecules as well as signaling [172].

The IgSF member JAM-A is a cellular receptor for both mammalian reovirus [19] and calicivirus [173]. JAM-A is a component of the tight junctions formed in both epithelial and endothelial cells [174, 175]. This homodimeric protein is formed by two monomers [176], and interactions between D1 domains generate a dimer interface. The homotrimeric reovirus attachment protein σ1 binds directly within the dimer interface of the membrane distal D1 domain of human JAM-A and disrupts the JAM-A–JAM-A interface [99, 169] as mutation of specific residues within the dimer interface reduce binding of the reovirus attachment protein σ1 [177]. Furthermore, all reovirus strains bind to JAM-A and require JAM-A as a receptor [178]. The σ1 protein is a homotrimeric protein comprised of large globular heads formed by an 8-stranded β barrel structure and long fibrous tails that comprised a triple beta-spiral motif [26, 179, 180]. The reovirus σ1 proteins among different strains represent the greatest sequence divergence, yet the β strand D and E (D–E loop) in the lower part of the globular head of σ1 are highly conserved among strains [179, 181]. The highly conserved D–E loop serves as the RBD for the serotype-independent receptor JAM-A, [99, 178]. Furthermore, the conserved interactions of σ1 with JAM-A extend to adenovirus fiber engagement of coxsackievirus and adenovirus receptor (CAR) [14].

The attachment protein of reovirus and adenovirus, their respective receptors, and the mechanism of receptor engagement bear a striking resemblance suggestive of an ancestral relationship between the dsRNA reovirus and dsDNA adenovirus [13]. Both attachment proteins, σ1 and fiber, are trimeric proteins that comprised large globular heads formed by an 8-stranded β barrel structure and long fibrous tails, referred to as the "knob" and "shaft" in adenovirus [179, 182] that insert into a pentameric protein at the fivefold axes of symmetry on the virion capsid [157]. CAR, like JAM-A, is also a homo-dimer comprised of two monomers, and fiber binds to the dimer interface region of CAR [99, 177, 183]. CAR, like JAM-A, also localizes to tight junctions of epithelial cells suggesting that viruses may bind directly to the dimer interface of tight junction proteins in order to disrupt cellular junctions thereby promoting viral invasion. The striking structural similarities in σ1–JAM-A and fiber–CAR interactions, as well as the attachment protein arrangement on the viral capsid, suggest evolutionary conservation of two quite divergent viruses [13, 14].

The interaction between reovirus σ1 and JAM-A is conserved among reovirus Type 1 (T1) and Type 3 (T3) strains [181]. In addition, both T1 and T3 reovirus strains also utilize the Nogo receptor 1 (NgR1) in particular cells, yet these interactions occur either through a distinct σ1 conformer or through the capsid protein σ3 [6]. Despite this conservation in receptor usage, the T1 and T3 reovirus strains differ in pathogenicity in the CNS of the mouse model, and these differences in reovirus pathogenesis have been well established to correlate with the S1 gene which encodes for σ1 [184, 185]. T1 strains target the ependymal cells in the CNS and cause hydrocephalus, while T3 strains target neurons and cause a lethal encephalitis [186]. Therefore, the conserved mechanisms of interactions between T1 and T3 σ1 with JAM-A suggest that

σ1 engagement of other receptors likely influences tissue tropism and disease pathogenesis. In fact, reovirus binding to SA receptors is also mediated by σ1 in the globular head domain in a region distinct from JAM-A binding [100, 101]. Interestingly, T1 and T3 reoviruses differ in their glycan receptor usage, as T1 reovirus utilizes the α2,3-linked GM2 glycan [101] and T3 reovirus utilizes the GM3 glycan, which contains α2,3-, α2,6-, and α2,8-linked SA [100]. Studies in the experimental mouse model demonstrate that glycan usage does dictate serotype-dependent disease outcomes as reovirus replication and virally induced hydrocephalus is more severe when σ1 binding to GM2 is not altered [187]. Moreover, mutation of SA binding residues in a T3 virus reduces reovirus replication and influences neurovirulence in neuronal cells in the CNS [188]. Thus, reovirus engages multiple receptors in order to mediate infection and the receptor interactions are largely associated with the σ1 attachment protein [100, 101, 181]. However, it is still not fully clear how the coordinated interactions of multiple receptors such as JAM-A and glycans in a particular target cell influence infection and pathogenesis. In the experimental mouse model of reovirus, endothelial expression of JAM-A is required for viremia and dissemination of reovirus in the bloodstream, yet JAM-A is not required for infection in the CNS [189]. Furthermore, infection of cortical neurons has been demonstrated to be independent of JAM-A and dependent on NgR1 [6]. Together, these findings suggest that reovirus utilizes multiple receptors to localize to various sites of infection within the host and cause disease.

Integrins

Integrins are integral membrane proteins that mediate a variety of functions including cell adhesion and signaling events [190]. Integrins are arranged as heterodimers on the cell surface composed of two transmembrane subunits: an α and a β subunit. The integrin heterodimers have a large extracellular domain to mediate binding to ligands such as extracellular membrane proteins including fibronectin or vitronectin either through the I- (or A) domain within the α subunit or through an interface formed by the β propeller domain of the α subunit with the I-domain of the β subunit [157, 190]. Oftentimes integrins recognize and bind to their ligands through short, linear integrin-binding motifs, such as the arginine–glycine–aspartic acid (RGD) motifs and Lys–Gly–Glu (KGE) motifs. Integrins have a short cytoplasmic domain that can elicit the activation of signaling pathways and can promote cytoskeletal rearrangement within the cells [157, 191].

A wide array of viruses utilize integrins as receptors to mediate multiple functions such as viral entry and activation of signaling events. The hMPV, an enveloped, negative-sense single-stranded RNA paramyxovirus and cause of respiratory infections particularly in children, utilizes integrins αvβ1 and α5β1 receptors to mediate infection through interactions with the viral fusion (F) protein [159, 192] The interaction between F and αvβ1 and α5β1 integrin receptors is mediated by the RGD motif found in F, which is conserved in hMPV strains [159]. Mutations within the RGD motif in F reduce infection [192, 193] and attenuate pathogenicity in cotton rats when introduced into a recombinant hMPV [192]. The interactions between integrins αvβ1 and α5β1 and the RGD motif in the F protein serve to mediate hMPV viral entry after initial binding to heparan sulfate [193, 194]. A number of other viruses utilize integrins as receptors [191] including HSV-2. Interactions of HSV-2 with αvβ3 integrin mediate viral entry and activate signaling pathways to release intracellular calcium stores from the endoplasmic reticulum and promote focal adhesion kinase (FAK) phosphorylation, which is necessary for viral entry, trafficking to the nucleus, and viral spread [195]. FMDV, a nonenveloped single-stranded RNA virus, has been reported to use αvβ1, αvβ3, αvβ6, and αvβ8 integrin receptors [160–164]. FMDV engages the αvβ6 integrin through a surface exposed flexible loop in VP1, referred to as the GH loop. As determined by high-resolution cryo-EM, binding to αvβ6 integrin is mediated by the RGD motif and surrounding hydrophobic residues in an extended form of the GH loop [164]. The enveloped single-stranded RNA flaviviruses WNV and Japanese encephalitis virus JEV utilize the receptor αvβ3 integrin in an RGD-independent manner [158] to mediate a post-attachment step in the virus life cycle [196]. However, some reports suggest that WNV infection can occur in an αvβ3 integrin-independent manner as well [197]. Lastly, entry of HSV is mediated by αvβ6 or αvβ8 integrins through interactions with the viral glycoprotein heterodimer gH/gL, and these interactions promote viral entry into the appropriate endocytic compartment [167]. The interaction of gH/gL with αvβ6 or αvβ8 integrins results in dissociation of gL from the virion, and gL release is necessary for activation of other viral glycoproteins necessary for viral entry [168]. Vial interactions with integrins are numerous and diverse, yet in some respects, the structural–functional relationship is conserved.

The structural and functional conservation of the reovirus σ1 interactions with JAM-A and adenovirus fiber interactions with CAR extend to the utilization of integrins as internalization receptors for both reovirus and adenovirus [13]. Integrins mediate internalization of adenovirus following binding to CAR [156, 157]. Adenovirus binds to CAR via the attachment protein fiber, which extends from the surface of the viral capsid at the five-fold vertices where the penton base protein resides. After initial binding to CAR, adenovirus binds to RGD-binding integrins including αv and β1 integrins through RGD motifs expressed

on penton base [156, 157]. Interestingly, mammalian reovirus internalization is also mediated by β1 integrins [153] following binding of the attachment protein σ1 to SA-containing glycans and JAM-A [198]. Furthermore, there are striking structural similarities between adenovirus fiber, which inserts into penton base at the fivefold axes of symmetry and σ1 that inserts into the pentameric protein λ2, which is a penton-base like protein [14, 157]. While a direct interaction between reovirus and integrins has not been established, there are RGD and KGE motifs expressed in the reovirus λ2 protein [153], suggesting that integrin interactions could be mediated through these binding sites, yet this requires further study. In addition to cell adhesion and entry, adenovirus–integrin interactions lead to fiber shedding and are thus critical in viral disassembly [199, 200]. Fiber shedding may be driven by induced conformational changes in penton base, which could allow the fivefold vertex to open and release fiber from the virion [201]. Integrin-mediated internalization of adenovirus via clathrin-mediated endocytosis and macropinocytosis requires PI3K activation and actin cytoskeleton reorganization through Rho family GTPases [202–204]. These elegant studies demonstrate how viruses can interact with integrins in a single or multiple receptor fashion, and each receptor is responsible for a myriad of functions essential to the infectious process.

Master locks: PtdSer viral receptors

PtdSer receptors, including T-cell immunoglobulin and mucin domain (TIM) and TYRO3, AXL, and the MERTK family of receptor tyrosine kinases (TAMs), have both been shown to serve as receptors for enveloped viruses from multiple virus families and viruses within the same viral family [25]. PtdSer receptors have been reported to mediate viral entry of a number of enveloped viruses including the filoviruses EBOV and Marburgvirus (MARV) [205]; flaviviruses WNV, [206], dengue virus (DENV) [24], and Zika virus (ZIKV) [207, 208]; and arenavirus Lassa Virus [209], and poxvirus vaccinia virus [210]. While these receptor families are distinct, they all recognize PtdSer on the viral envelope of enveloped viruses and mediate viral attachment, entry, and/or activation of signaling events [24, 25, 206, 208]. Following internalization into the endocytic compartment, some filoviruses including EBOV and MARV also require engagement of Niemann-Pick C1 receptor in the endo-lysosome via a proteolytically primed glycoprotein providing yet another layer of complexity and security in receptor engagement at a late entry step [10].

PtdSer is normally expressed on the inner leaflet of the plasma membrane of living cells. However, PtdSer becomes exposed in necrotic or apoptotic cells, and the exposure of PtdSer allows for phagocytic cells to recognize and remove dead cells [25, 211]. PtdSer binding to the PtdSer receptors can occur either through a direct interaction or through a ligand that binds directly to PtdSer and the receptor, acting as a bridge [23, 24]. PtdSer receptors that enhance virus entry have been termed PtdSer-mediated virus entry enhancing receptors PVEERs [25]. Enveloped viruses with PtdSer expressed on the viral envelope appear like apoptotic bodies and can be recognized by PVEERS and “trick” the cell into to engulfing it through phagocytosis; the usage of cell clearance mechanisms to invade cells has been likened to apoptotic mimicry [25]. As enveloped viruses bud from host cells and pinch off a portion of the plasma membrane, where the PtdSer is located on the inner leaflet, it begs the question: *how does the membrane get flipped inside out so that the PtdSer can be surface expressed on the virion envelope*? An interesting new finding suggests that EBOV, which has been demonstrated to utilize the TIM-1 and TAM receptor AXL [205, 212, 213] requires the XK-related protein (Xkr) 8 scramblase to expose the PtdSer and disguise the virus as an apoptotic cell [214]. In fact, the Xkr8 traffics with EBOV to sites of budding and gets incorporated into EBOV virus-like particles, and thereby enhances EBOV entry in a PtdSer-dependent manner [214]. However, it should be noted that the presence of PtdSer alone is not sufficient for enveloped viral entry by apoptotic mimicry, as entry of viruses with PtdSer-expressing envelopes including IAV, vesicular stomatitis virus, and coronaviruses is not enhanced by PVEERS [25]. Thus, while a growing number of enveloped viruses utilize a common mechanism to enter cells through PtdSer receptors, the presence of the viral glycoprotein and cell type-dependent differences influence this process [25].

PVEERS have been demonstrated to mediate viral entry and infection of flaviviruses WNV, DENV, and ZIKV. Flaviviruses belong to the *Flaviviridae* family, a genus that comprised over 70 small, enveloped viruses with positive-sense single stranded RNA genomes [215]. The flavivirus E glycoprotein mediates interactions with cellular receptors and entry is mediated by endocytosis [207, 216]. While flaviviruses exhibit differences in tissue tropism and can lead to a range of diseases, there is considerable redundancy in receptor usage and function. WNV, DENV, and ZIKV are transmitted through the arthropod vectors mosquitoes [215]. The incidence in flavivirus infections has risen in recent years and has been a source of significant human health conditions. WNV is asymptomatic in the majority of individuals, but causes WNV fever and neuroinvasive disease in some, and has caused outbreaks in Europe, Africa, Asia, and North and South America [217]. Zika virus (ZIKV) has reemerged in recent years in parts of North, Central, and South Americas, and while usually asymptomatic, can cause neurological disease, Guillain–Barré syndrome, and congenital

ZIKV infections that can result in microcephaly and abortion [218]. DENV infects up to 100 million people annually in the Western Pacific Region including China and causes a self-limiting infection in most but can result in the more serious dengue hemorrhagic fever [219]. The increase in recent flavivirus outbreaks and new information regarding PVEERS as common receptors for these viruses suggest that this shared common mechanism of viral entry could be a potential site for exploitation by an anti-viral strategy.

ZIKV infection of dermal fibroblasts, epidermal keratinocytes, and immature dendritic cells has been shown to be mediated by several possible receptors including DC-SIGN, as well as the TAM family members Tyro 3 and AXL [207]. ZIKV infection of glial cells, astrocytes, and microglial cells has also recently been demonstrated to be mediated by AXL. Interestingly, other TIM and TAM family members serve as receptors for flaviviruses [24, 208]. AXL is also an entry receptor for DENV [24]. AXL-mediated entry of both ZIKV and DENV is mediated through Gas6, an AXL ligand that binds directly to phosphatidlyserine expressed on the viral envelope and binds to AXL. This binding event leads to AXL-mediated entry of ZIKV and DENV, yet AXL also induces the activation of tyrosine kinase signaling that modulates innate immune signaling through interferon (IFN) [24, 206, 208]. However, conflicting reports suggest that AXL is not required for ZIKV infection in mice [220] or neural progenitor cells [221]. Furthermore, while AXL was reported as an entry receptor in astrocytes and microglial cells, others have reported that AXL does not mediate ZIKV entry in astrocytes, but specifically activates type 1 IFN signaling through the type 1 IFN receptor to activate several IFNs and IFN-stimulating genes, including the type 1 IFN signaling suppressor [222]. ZIKV infection also induces IFN-stimulated genes in human skin cells [207]. Despite these conflicting findings on the role for AXL in ZIKV entry of astrocytes, infection of human umbilical fetal endothelial cells, a major component of the placental barrier, is dependent on AXL–Gas6 interactions [223]. Taken together, despite investigator-reported differences in AXL dependency in ZIKV infection of particular cell types, these findings suggest an important role for AXL in human fetal endothelial cells [223]. These data are important given the devastating pathogenicity in the fetus and resultant congenital complications such as microcephaly. Furthermore, AXL-induced downmodulation of the type I IFN signaling pathway demonstrates how viruses can dampen the innate immune signaling pathway to facilitate viral infection [24, 208, 222].

Breaking down the door: how viruses overcome multiple locks/receptors

As highlighted throughout this review and the literature, many viruses must utilize multiple receptors in order to efficiently invade cells. Furthermore, in many cases, viruses utilize cell-type specific receptors, thereby lending additional restrictions to tropism. How do viruses overcome multiple locks/receptors to orchestrate the events of viral attachment, entry, and signaling? These questions have been some of the most challenging to address in the field of virus–receptor interactions because while these steps are considered isolated and distinct, it is difficult to isolate these steps using current techniques in the laboratory. For instance, if a virus must first interact with a receptor in order to then undergo a conformational change for downstream steps in the virus life cycle or to mediate secondary interactions with another receptor, one could not inhibit the first receptor event and study the second event as infection would be halted. On the other hand, these negative results would not be sufficient to conclude that the initial interaction is necessary for the next. In addition, in many cases, virus interactions with a single receptor can have multiple effects on the cell such as induction of entry strategies and activation of signaling pathways. However, some elegant studies have provided insight into the mechanisms by which viruses engage multiple cell-surface receptors to mediate infection, or open several locks to break down the door.

HIV requires the IgSF member CD4 as the primary receptor but also requires specific coreceptors CCR4 and CXCR5 [224]. The HIV envelope (ENV) glycoprotein interacts with CD4 [149, 225, 226] to mediate specific interactions between ENV and CD4 that are required for infection [224]. However, initial interactions between ENV and host cells occur via nonspecific cellular receptors including heparan sulfate proteoglycans [227] or specific receptors such as α4β7 integrin [228] or the innate immune receptor DC-SIGN [229]. ENV is a trimeric protein composed of gp120 and gp41, and gp120 mediates binding to CD4 through conserved domains leading to conformational changes within gp120 and CD4 [224]. Following CD4 interactions, HIV requires binding to the chemokine coreceptors CXCR4 or CCR5 in macrophages and $CD4^+$ T cells, respectively [230, 231]. CXCR4 and CCR5 are G-protein coupled receptors (GPCRs) [230], which play various roles in attachment and entry of a number of viruses [145, 232, 233]. Coreceptor interactions are necessary for viral entry and fusion, which is facilitated by gp41 [230]. The importance of HIV coreceptors in viral infection is well documented to play important regulator roles in HIV infection and dictate tissue tropism, in respective cell types [231]. Interestingly, individuals that are homozygous for the polymorphism in *CCR5 (*ccr5Δ32) are highly resistant to HIV infection and heterozygosity results in "long-term nonprogressors" *of HIV infection* demonstrating the importance of viral co-receptor expression in tissue tropism and viral pathogenesis *in vivo* [234, 235]. Furthermore, Maraviroc, a CCR5 antagonist that blocks HIV entry, is approved by the Food and Drug Administration and

European Medicines Agency for R5-tropic HIV [235]. Maraviroc binding to CCR5 induces a conformational change in the receptor that inhibits interactions with gp120 and blocks viral entry [236]. Maraviroc has demonstrated efficacy *in vivo* leading to reduced viral loads and increased $CD4^+$ T cells [237]. Furthermore, Maraviroc has been demonstrated to be an effective latency reversal agent to activate reservoirs of latent virus that cannot be eliminated using current antiretroviral treatments [238]. Thus, Maraviroc can be utilized as an entry inhibitor but also as a latency reversal agent in therapeutic drug combinations to treat HIV infection [237, 238].

Group B CVBs require multiple receptors in order to invade epithelial cells including IgSF member CAR and decay-accelerating factor (DAF) (CD55) [147]. CVBs utilize the CAR, which is expressed in the tight junctions of epithelial cells, and would be relatively inaccessible to a virus. However, CVBs first bind to DAF on the apical cell surface of polarized cells, and this binding event leads to DAF clustering and activation of Abl kinase, which regulates actin rearrangement that allows for opening of the tight junction and thus viral movement into the junction. CVB–DAF interactions also activate Fyn kinase, which is necessary for viral entry and transport within caveolin-rich vesicles [147]. Once localized in the junction, CVB interacts with CAR, which induces conformational changes in the capsid that are also required for viral entry [147]. These findings demonstrate how a virus can utilize a primary receptor to activate signaling pathways and disrupt the cellular architecture, which is necessary to facilitate interactions with a secondary receptor that is required for viral entry.

Furthermore, JCPyV requires α2,6-linked LSTc in order to attach to host cells. However, while this binding event is highly specific, it is not sufficient to mediate viral infection. Cells that express α2,6 SA alone cannot support infection suggesting that JCPyV requires multiple receptors [135]. Experimental cell line HEK293A cells, which express α2,6-LSTc on the cell surface, cannot be productively infected by JCPyV [145]. In fact, viral attachment is dependent on α2,6-LSTc, but infection is only conferred upon expression of the serotonin 5-HT_2Rs [145]. Expression of 5-HTRs of the 2 subtype (2A, 2B, and 2C) confers infection in this otherwise poorly permissive cell line, and HEK293A cells stably expressing the 5-HT_2Rs demonstrate significantly enhanced viral internalization [145]. The mechanism by which JCPyV utilizes the 5-HT_2Rs to mediate viral entry is not fully understood and requires further study.

Perspectives

Research to elucidate how viruses interact with host cell receptors is critical to understand how viruses invade host cells and to define how these interactions specify tissue tropism and influence disease outcomes. While the available data provide significant insights into the mechanisms of viral attachment and entry, this information is confounded by several challenges including multiple receptor usage, cell-type dependent differences in receptor expression and utilization, strain or serotype-dependent usage of specific viral receptors, the use of laboratory-generated experimental virus models, and lack of tractable model systems for some viruses. Moreover, while virus interactions with attachment and entry receptors regulate many essential steps in viral infection, it is not the sole determinant of tissue tropism, viral spread, or pathogenesis. In fact, there are numerous studies establishing that viruses including influenza virus and HIV can spread from cell to cell through receptor-independent mechanisms such as through tunneling nanotubes [239–241] . Continued research in the area of viral-induced tunneling nanotubes will yield a new area of study for the field that will improve our understanding of receptor-independent viral spread and host immune evasion, a complication of antiviral treatments. Overall the study of virus–receptor interactions is promising for the development of new antiviral therapies, yet oftentimes laboratory-based discoveries have not translated well into the clinic. However, the challenges of translation medicine and bringing compounds from bench to bedside are not unique to the development of antiviral therapies. It is essential to overcome these challenges in order to improve our current understanding of virus–receptor interactions and be able to apply this knowledge to the future development of antiviral therapies, as some novel therapeutics in development targeting virus–receptor interactions provide great promise. For example, highlighted throughout this review are several examples of overlapping cell attachment and entry mechanisms utilized by many different viruses, such as utilization of SA receptors, IgSF members, and PtdSer receptors, which could be a target for the development of antiviral therapies such as inhibitors and mAbs that could be applied to other viruses.

GPCR agonists and antagonists block infection of a wide range of viruses by specifically blocking viral entry suggesting the utilization of common GPCR-mediated pathways that could be exploited for the development of antiviral therapies. Viral entry of a number of other viruses has been demonstrated to be selectively inhibited by serotonin 5-HT receptor agonists and antagonists including JCPyV, reovirus, chikungunya virus, coronavirus mouse hepatitis virus, and filoviruses EBOV and MARV [232, 233]. Reovirus is selectively inhibited by 5-nonyloxytryptamine, 5-nonyloxytryptamine a 5-HTR agonist that specifically alters the cellular distribution of early endosomes and viral trafficking to the late endosomes, which are necessary for the process of reovirus uncoating [232].

A range of 5-HTR antagonists and other GPCR antagonists were determined to block EBOV and MARV infection through a GPCR inhibitor library screen [233]. EBOV and MARV attachment to host cells was unaffected by GPCR antagonists, but there was a block in viral entry prior to viral fusion events [233]. Moreover, dopamine receptors, which are also GPCRs, increase HIV replication in macrophages by specifically increasing HIV entry, although this entry still requires CCR5 activity [242]. These data suggest that many viruses utilize GPCR-mediated pathways and that targeting these pathways may serve as a novel, broad-spectrum antiviral, capable of targeting a number of viruses including those with significant morbidity and mortality such as EBOV and MARV.

Monoclonal antibodies that disrupt virus–receptor interactions represent a promising new class of drugs against viral infection for HIV, ZIKV, and JCPyV-induced PML [40, 42, 243]. The anti-CD4 mAb ibalizumab binds to domain 2 of CD4 receptor and induces conformational changes that block HIV entry and fusion, and this is an effective new treatment especially for multidrug-resistant HIV-infected patients [42]. Moreover, a broadly neutralizing antibody that recognizes a highly conserved fusion loop of ZIKV E can neutralize ZIKV in mouse models [243]. In addition, recent studies to identify a treatment for JCPyV-induced PML demonstrate that the most promising candidates are mAbs that target viral capsid protein VP1 and vaccines that stimulate VP1-based immunity [41]. These treatments likely lead to neutralization of circulating virus and prevent JCPyV binding to receptors on host cells. Furthermore, development of drugs that could inhibit receptors with great redundancy in viral utilization such as PtdSer inhibitors that could block a range of viruses including EBOV, WNV, or ZIKV, through inhibition of Gas6 ligand presentation to PtdSer receptors through small-molecular inhibitors [208, 244, 245]. However, the development of new therapies that are effective and nontoxic must be preceded by the elegant molecular studies of viral attachment and entry that are currently ongoing in the field and will serve as the basis for new therapies in viral disease treatment highlighting the continued importance of basic molecular biology research.

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Abbreviations used:
HIV, human immunodeficiency virus; EBOV, Ebola virus; SAs, sialic acids; CAMs, cellular adhesion molecules; PtdSer, phosphatidylserine; Neu5Ac, 5-*N*-acetyl neuraminic acid; IAV, influenza A virus; MERS-CoV, Middle East Respiratory Syndrome coronavirus; HA, hemagglutinin; NA, neuraminidase; RBD, receptor-binding domain; JAM-A, junctional adhesion molecule A; BKPyV, BK polyomavirus; CNS, central nervous system; PML, progressive multifocal leukoencephalopathy; SV40, Simian virus 40; VP1, viral protein 1; PI3K, phosphatidylinositol 3-kinase; IgSF, immunoglobulin superfamily; CAMs, cell adhesion molecules; CVB, coxsackievirus B; WNV, West Nile virus; hMPV, human metapneuomovirus; FMDV, foot-and-mouth disease virus; HSV, herpes simplex virus; CAR, coxsackievirus and adenovirus receptor; RGD, arginine–glycine–aspartic acid; IFN, interferon; GPCRs, G-protein coupled receptors; DAF, decay-accelerating factor; JCPyV, JC polyomavirus; LSTc, lactoseries tetrasaccharide c; 5-HT, 5-hydroxytryptamine.

References

[1] J. Grove, M. Marsh, The cell biology of receptor-mediated virus entry, J. Cell Biol. 195 (2011) 1071–1082.
[2] M. Marsh, A. Helenius, Virus entry: open sesame, Cell 124 (2006) 729–740.

[3] U. Neu, S.A. Allen, B.S. Blaum, Y. Liu, M. Frank, A.S. Palma, et al., A structure-guided mutation in the major capsid protein retargets BK polyomavirus, PLoS Pathog. 9 (2013), e1003688.
[4] K.M. Guglielmi, E.M. Johnson, T. Stehle, T.S. Dermody, Attachment and cell entry of mammalian orthoreovirus, Curr. Top. Microbiol. Immunol. 309 (2006) 1–38.
[5] E.S. Barton, J.C. Forrest, J.L. Connolly, J.D. Chappell, Y. Liu, F.J. Schnell, et al., Junction adhesion molecule is a receptor for reovirus, Cell 104 (2001) 441–451.
[6] J.L. Konopka-Anstadt, B.A. Mainou, D.M. Sutherland, Y. Sekine, S.M. Strittmatter, T.S. Dermody, The Nogo receptor NgR1 mediates infection by mammalian reovirus, Cell Host Microbe 15 (2014) 681–691.
[7] A. Takada, C. Robison, H. Goto, A. Sanchez, K.G. Murti, M.A. Whitt, et al., A system for functional analysis of Ebola virus glycoprotein, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 14764–14769.
[8] R.J. Wool-Lewis, P. Bates, Characterization of Ebola virus entry by using pseudotyped viruses: identification of receptor-deficient cell lines, J. Virol. 72 (1998) 3155–3160.
[9] J. Cronin, X.Y. Zhang, J. Reiser, Altering the tropism of lentiviral vectors through pseudotyping, Curr. Gene Ther. 5 (2005) 387–398.
[10] E.H. Miller, G. Obernosterer, M. Raaben, A.S. Herbert, M.S. Deffieu, A. Krishnan, et al., Ebola virus entry requires the host-programmed recognition of an intracellular receptor, EMBO J. 31 (2012) 1947–1960.
[11] U. Neu, T. Stehle, W.J. Atwood, The Polyomaviridae: contributions of virus structure to our understanding of virus receptors and infectious entry, Virology 384 (2009) 389–399.
[12] U. Neu, J. Bauer, T. Stehle, Viruses and sialic acids: rules of engagement, Curr. Opin. Struct. Biol. 21 (2011) 610–618.
[13] T. Stehle, T.S. Dermody, Structural evidence for common functions and ancestry of the reovirus and adenovirus attachment proteins, Rev. Med. Virol. 13 (2003) 123–132.
[14] T. Stehle, T.S. Dermody, Structural similarities in the cellular receptors used by adenovirus and reovirus, Viral Immunol. 17 (2004) 129–143.
[15] L.J. Stroh, T. Stehle, Glycan engagement by viruses: receptor switches and specificity, Ann. Rev. Virol. 1 (2014) 285–306.
[16] Y. Yamauchi, A. Helenius, Virus entry at a glance, J. Cell Sci. 126 (2013) 1289–1295.
[17] T.S. Dermody, E. Kirchner, K.M. Guglielmi, T. Stehle, Immunoglobulin superfamily virus receptors and the evolution of adaptive immunity, PLoS Pathog. 5 (2009), e1000481.
[18] J.E. Stencel-Baerenwald, K. Reiss, D.M. Reiter, T. Stehle, T.S. Dermody, The sweet spot: defining virus–sialic acid interactions, Nat. Rev. Microbiol. 12 (2014) 739–749.
[19] E.S. Barton, J.L. Connolly, J.C. Forrest, J.D. Chappell, T.S. Dermody, Utilization of sialic acid as a coreceptor enhances reovirus attachment by multistep adhesion strengthening, J. Biol. Chem. 276 (2001) 2200–2211.
[20] J.M. Bergelson, J.A. Cunningham, G. Droguett, E.A. Kurt-Jones, A. Krithivas, J.S. Hong, et al., Isolation of a common receptor for Coxsackie B viruses and adenoviruses 2 and 5, Science (New York, N.Y.) 275 (1997) 1320–1323.
[21] R.P. Tomko, R. Xu, L. Philipson, HCAR and MCAR: the human and mouse cellular receptors for subgroup C adenoviruses and group B coxsackieviruses, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 3352–3356.
[22] D. Bhella, The role of cellular adhesion molecules in virus attachment and entry, Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 370 (2015) 20140035.
[23] K. Morizono, Y. Xie, T. Olafsen, B. Lee, A. Dasgupta, A.M. Wu, et al., The soluble serum protein Gas6 bridges virion envelope phosphatidylserine to the TAM receptor tyrosine kinase Axl to mediate viral entry, Cell Host Microbe 9 (2011) 286–298.
[24] L. Meertens, X. Carnec, M.P. Lecoin, R. Ramdasi, F. Guivel-Benhassine, E. Lew, et al., The TIM and TAM families of phosphatidylserine receptors mediate dengue virus entry, Cell Host Microbe 12 (2012) 544–557.
[25] S. Moller-Tank, W. Maury, Phosphatidylserine receptors: enhancers of enveloped virus entry and infection, Virology 468-470 (2014) 565–580.
[26] T. Stehle, Z.M. Khan, Rules and exceptions: sialic acid variants and their role in determining viral tropism, J. Virol. 88 (2014) 7696–7699.
[27] A. Varki, R. Schauer, Sialic acids, in: A. Varki, R.D. Cummings, J.D. Esko, H.H. Freeze, P. Stanley, C.R. Bertozzi, et al., (Eds.), Essentials of Glycobiology, 2nd ed. Cold Spring Harbor Laboratory Press, NY, 2009.
[28] Y. Li, X. Chen, Sialic acid metabolism and sialyltransferases: natural functions and applications, Appl. Microbiol. Biotechnol. 94 (2012) 887–905.
[29] R. Schauer, Sialic acids as regulators of molecular and cellular interactions, Curr. Opin. Struct. Biol. 19 (2009) 507–514.
[30] T.K. Altheide, T. Hayakawa, T.S. Mikkelsen, S. Diaz, N. Varki, A. Varki, System-wide genomic and biochemical comparisons of sialic acid biology among primates and rodents: evidence for two modes of rapid evolution, J. Biol. Chem. 281 (2006) 25689–25702.
[31] R.K. Yu, Y.T. Tsai, T. Ariga, M. Yanagisawa, Structures, biosynthesis, and functions of gangliosides—an overview, J. Oleo Sci. 60 (2011) 537–544.
[32] H.J. Maccioni, R. Quiroga, M.L. Ferrari, Cellular and molecular biology of glycosphingolipid glycosylation, J. Neurochem. 117 (2011) 589–602.
[33] M.A. Simpson, H. Cross, C. Proukakis, D.A. Priestman, D.C. Neville, G. Reinkensmeier, et al., Infantile-onset symptomatic epilepsy syndrome caused by a homozygous loss-of-function mutation of GM3 synthase, Nat. Genet. 36 (2004) 1225–1229.
[34] K. Sandhoff, K. Harzer, Gangliosides and gangliosidoses: principles of molecular and metabolic pathogenesis, J. Neurosci. 33 (2013) 10195–10208.
[35] W. Li, R.J.G. Hulswit, I. Widjaja, V.S. Raj, R. Mcbride, W. Peng, et al., Identification of sialic acid-binding function for the Middle East respiratory syndrome coronavirus spike glycoprotein, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) (E8508-E17).
[36] M. de Graaf, R.A. Fouchier, Role of receptor binding specificity in influenza A virus transmission and pathogenesis, EMBO J. 33 (2014) 823–841.
[37] Y. Shi, Y. Wu, W. Zhang, J. Qi, G.F. Gao, Enabling the 'host jump': structural determinants of receptor-binding specificity in influenza A viruses, Nat. Rev. Microbiol. 12 (2014) 822–831.
[38] U. Neu, M.S. Maginnis, A.S. Palma, L.J. Stroh, C.D. Nelson, T. Feizi, et al., Structure–function analysis of the human JC polyomavirus establishes the LSTc pentasaccharide as a functional receptor motif, Cell Host Microbe 8 (2010) 309–319.
[39] J. Sui, W. Li, A. Murakami, A. Tamin, L.J. Matthews, S.K. Wong, et al., Potent neutralization of severe acute

respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 2536–2541.
[40] I. Jelcic, B. Combaluzier, I. Jelcic, W. Faigle, L. Senn, B.J. Reinhart, et al., Broadly neutralizing human monoclonal JC polyomavirus VP1-specific antibodies as candidate therapeutics for progressive multifocal leukoencephalopathy, Sci. Transl. Med. 7 (2015), 306ra150.
[41] C.L. Mayberry, C.D.S. Nelson, M.S. Maginnis, JC polyomavirus attachment and entry: potential sites for PML therapeutics, Curr. Clin. Microbiol. Rep. 4 (2017) 132–141.
[42] S.A. Iacob, D.G. Iacob, Ibalizumab targeting CD4 receptors, an emerging molecule in HIV therapy, Front. Microbiol. 8 (2017) 2323.
[43] O. Oyelaran, J.C. Gildersleeve, Glycan arrays: recent advances and future challenges, Curr. Opin. Chem. Biol. 13 (2009) 406–413.
[44] D.F. Smith, R.D. Cummings, Investigating virus–glycan interactions using glycan microarrays, Curr. Opin. Virol. 7 (2014) 79–87.
[45] O. Blixt, S. Head, T. Mondala, C. Scanlan, M.E. Huflejt, R. Alvarez, et al., Printed covalent glycan array for ligand profiling of diverse glycan binding proteins, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 17033–17038.
[46] R.A. Alvarez, O. Blixt, Identification of ligand specificities for glycan-binding proteins using glycan arrays, Methods Enzymol. 415 (2006) 292–310.
[47] R. Raman, M. Venkataraman, S. Ramakrishnan, W. Lang, S. Raguram, R. Sasisekharan, Advancing glycomics: implementation strategies at the consortium for functional glycomics, Glycobiology 16 (2006) 82R–90R.
[48] N. Zhao, B.E. Martin, C.K. Yang, F. Luo, X.F. Wan, Association analyses of large-scale glycan microarray data reveal novel host-specific substructures in influenza A virus binding glycans, Sci. Rep. 5 (2015) 15778.
[49] P.F.N.G. Wright, Y. Kawaoka, Orthomyxoviruses, Lippincott Williams & Wilkins, 2013.
[50] S.J. Gamblin, J.J. Skehel, Influenza hemagglutinin and neuraminidase membrane glycoproteins, J. Biol. Chem. 285 (2010) 28403–28409.
[51] L. Gillespie, P. Roosendahl, W.C. Ng, A.G. Brooks, P.C. Reading, S.L. Londrigan, Endocytic function is critical for influenza A virus infection via DC-SIGN and L-SIGN, Sci. Rep. 6 (2016) 19428.
[52] E. de Vries, D.M. Tscherne, M.J. Wienholts, V. Cobos-Jimenez, F. Scholte, A. Garcia-Sastre, et al., Dissection of the influenza A virus endocytic routes reveals macropinocytosis as an alternative entry pathway, PLoS Pathog. 7 (2011), e1001329.
[53] J.J. Skehel, D.C. Wiley, Receptor binding and membrane fusion in virus entry: the influenza hemagglutinin, Annu. Rev. Biochem. 69 (2000) 531–569.
[54] J.K. Taubenberger, J.C. Kash, Influenza virus evolution, host adaptation, and pandemic formation, Cell Host Microbe 7 (2010) 440–451.
[55] C.R. Parrish, P.R. Murcia, E.C. Holmes, Influenza virus reservoirs and intermediate hosts: dogs, horses, and new possibilities for influenza virus exposure of humans, J. Virol. 89 (2015) 2990–2994.
[56] C.E. van de Sandt, J.H. Kreijtz, G.F. Rimmelzwaan, Evasion of influenza A viruses from innate and adaptive immune responses, Viruses 4 (2012) 1438–1476.
[57] E.J. Schrauwen, M. de Graaf, S. Herfst, G.F. Rimmelzwaan, A.D. Osterhaus, R.A. Fouchier, Determinants of virulence of influenza A virus, Eur. J. Clin. Microbiol. Infect. Dis. 33 (2014) 479–490.
[58] R. Gao, B. Cao, Y. Hu, Z. Feng, D. Wang, W. Hu, et al., Human infection with a novel avian-origin influenza A (H7N9) virus, N. Engl. J. Med. 368 (2013) 1888–1897.
[59] CDC, Asian Lineage Avian Influenza A (H7N9) Virus, 2018.
[60] J.D. Mathews, J.M. Chesson, J.M. Mccaw, J. Mcvernon, Understanding influenza transmission, immunity and pandemic threats, Influenza Other Respir. Viruses 3 (2009) 143–149.
[61] K. Shinya, Y. Kawaoka, Influenza virus receptors in the human airway, Uirusu 56 (2006) 85–89.
[62] A. Garcia-Sastre, Influenza virus receptor specificity: disease and transmission, Am. J. Pathol. 176 (2010) 1584–1585.
[63] W. Ma, K.M. Lager, A.L. Vincent, B.H. Janke, M.R. Gramer, J.A. Richt, The role of swine in the generation of novel influenza viruses, Zoonoses Public Health 56 (2009) 326–337.
[64] M. Franca, D.E. Stallknecht, R. Poulson, J. Brown, E.W. Howerth, The pathogenesis of low pathogenic avian influenza in mallards, Avian Dis. 56 (2012) 976–980.
[65] L.M. Chen, P. Rivailler, J. Hossain, P. Carney, A. Balish, I. Perry, et al., Receptor specificity of subtype H1 influenza A viruses isolated from swine and humans in the United States, Virology 412 (2011) 401–410.
[66] K.C. Bradley, S.E. Galloway, Y. Lasanajak, X. Song, J. Heimburg-Molinaro, H. Yu, et al., Analysis of influenza virus hemagglutinin receptor binding mutants with limited receptor recognition properties and conditional replication characteristics, J. Virol. 85 (2011) 12387–12398.
[67] L.M. Chen, O. Blixt, J. Stevens, A.S. Lipatov, C.T. Davis, B.E. Collins, et al., In vitro evolution of H5N1 avian influenza virus toward human-type receptor specificity, Virology 422 (2012) 105–113.
[68] S.K. Chothe, G. Bhushan, R.H. Nissly, Y.T. Yeh, J. Brown, G. Turner, et al., Avian and human influenza virus compatible sialic acid receptors in little brown bats, Sci. Rep. 7 (2017) 660.
[69] W. Ma, A. Garcia-Sastre, M. Schwemmle, Expected and unexpected features of the newly discovered bat influenza A-like viruses, PLoS Pathog. 11 (2015), e1004819.
[70] Z.A. Memish, N. Mishra, K.J. Olival, S.F. Fagbo, V. Kapoor, J.H. Epstein, et al., Middle East respiratory syndrome coronavirus in bats, Saudi Arabia, Emerg. Infect. Dis. 19 (2013) 1819–1823.
[71] C.E. Brook, A.P. Dobson, Bats as 'special' reservoirs for emerging zoonotic pathogens, Trends Microbiol. 23 (2015) 172–180.
[72] H.A. Mohd, J.A. Al-Tawfiq, Z.A. Memish, Middle East respiratory syndrome coronavirus (MERS-CoV) origin and animal reservoir, Virol. J. 13 (2016) 87.
[73] E. Bottcher-Friebertshauser, H.D. Klenk, W. Garten, Activation of influenza viruses by proteases from host cells and bacteria in the human airway epithelium, Pathog. Dis. 69 (2013) 87–100.
[74] R. Xu, R. Mcbride, C.M. Nycholat, J.C. Paulson, I.A. Wilson, Structural characterization of the hemagglutinin receptor specificity from the 2009 H1N1 influenza pandemic, J. Virol. 86 (2012) 982–990.
[75] T. Lin, G. Wang, A. Li, Q. Zhang, C. Wu, R. Zhang, et al., The hemagglutinin structure of an avian H1N1 influenza A virus, Virology 392 (2009) 73–81.
[76] J. Liu, D.J. Stevens, L.F. Haire, P.A. Walker, P.J. Coombs, R.J. Russell, et al., Structures of receptor complexes formed

by hemagglutinins from the Asian influenza pandemic of 1957, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 17175–17180.
[77] J. Cui, N. Qu, Y. Guo, L. Cao, S. Wu, K. Mei, et al., Phylogeny, pathogenicity, and transmission of H5N1 avian influenza viruses in chickens, Front. Cell. Infect. Microbiol. 7 (2017) 328.
[78] M. Imai, Y. Kawaoka, The role of receptor binding specificity in interspecies transmission of influenza viruses, Curr. Opin. Virol. 2 (2012) 160–167.
[79] X. Xiong, P.J. Coombs, S.R. Martin, J. Liu, H. Xiao, J.W. Mccauley, et al., Receptor binding by a ferret-transmissible H5 avian influenza virus, Nature 497 (2013) 392–396.
[80] S. Herfst, M. Imai, Y. Kawaoka, R.A. Fouchier, Avian influenza virus transmission to mammals, Curr. Top. Microbiol. Immunol. 385 (2014) 137–155.
[81] M. Matrosovich, A. Tuzikov, N. Bovin, A. Gambaryan, A. Klimov, M.R. Castrucci, et al., Early alterations of the receptor-binding properties of H1, H2, and H3 avian influenza virus hemagglutinins after their introduction into mammals, J. Virol. 74 (2000) 8502–8512.
[82] Y. Shi, W. Zhang, F. Wang, J. Qi, Y. Wu, H. Song, et al., Structures and receptor binding of hemagglutinins from human-infecting H7N9 influenza viruses, Science (New York, N.Y.) 342 (2013) 243–247.
[83] WHO, Middle East respiratory syndrome coronavirus (MERS-CoV)—Saudi Arabia, 2018.
[84] S. van Boheemen, M. de Graaf, C. Lauber, T.M. Bestebroer, V.S. Raj, A.M. Zaki, et al., Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans, MBio 3 (2012).
[85] A.M. Zaki, S. van Boheemen, T.M. Bestebroer, A.D. Osterhaus, R.A. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med. 367 (2012) 1814–1820.
[86] R.J. Hulswit, C.A. de Haan, B.J. Bosch, Coronavirus spike protein and tropism changes, Adv. Virus Res. 96 (2016) 29–57.
[87] Z.A. Memish, M. Cotten, B. Meyer, S.J. Watson, A.J. Alsahafi, A.A. Al Rabeeah, et al., Human infection with MERS coronavirus after exposure to infected camels, Saudi Arabia, 2013, Emerg. Infect. Dis. 20 (2014) 1012–1015.
[88] H. Mou, V.S. Raj, F.J. van Kuppeveld, P.J. Rottier, B.L. Haagmans, B.J. Bosch, The receptor binding domain of the new Middle East respiratory syndrome coronavirus maps to a 231-residue region in the spike protein that efficiently elicits neutralizing antibodies, J. Virol. 87 (2013) 9379–9383.
[89] F. Li, Receptor recognition mechanisms of coronaviruses: a decade of structural studies, J. Virol. 89 (2015) 1954–1964.
[90] R.N. Kirchdoerfer, C.A. Cottrell, N. Wang, J. Pallesen, H.M. Yassine, H.L. Turner, et al., Pre-fusion structure of a human coronavirus spike protein, Nature 531 (2016) 118–121.
[91] A.C. Walls, M.A. Tortorici, B.J. Bosch, B. Frenz, P.J.M. Rottier, F. Dimaio, et al., Cryo-electron microscopy structure of a coronavirus spike glycoprotein trimer, Nature 531 (2016) 114–117.
[92] F. Li, W. Li, M. Farzan, S.C. Harrison, Structure of SARS coronavirus spike receptor-binding domain complexed with receptor, Science (New York, N.Y.) 309 (2005) 1864–1868.
[93] G. Peng, D. Sun, K.R. Rajashankar, Z. Qian, K.V. Holmes, F. Li, Crystal structure of mouse coronavirus receptor-binding domain complexed with its murine receptor, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 10696–10701.
[94] G. Lu, Y. Hu, Q. Wang, J. Qi, F. Gao, Y. Li, et al., Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26, Nature 500 (2013) 227–231.
[95] Y. Chen, K.R. Rajashankar, Y. Yang, S.S. Agnihothram, C. Liu, Y.L. Lin, et al., Crystal structure of the receptor-binding domain from newly emerged Middle East respiratory syndrome coronavirus, J. Virol. 87 (2013) 10777–10783.
[96] N. Wang, X. Shi, L. Jiang, S. Zhang, D. Wang, P. Tong, et al., Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4, Cell Res. 23 (2013) 986–993.
[97] V.S. Raj, H. Mou, S.L. Smits, D.H. Dekkers, M.A. Muller, R. Dijkman, et al., Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC, Nature 495 (2013) 251–254.
[98] J.A. Al-Tawfiq, Z.A. Memish, Infection control measures for the prevention of MERS coronavirus transmission in healthcare settings, Expert Rev. Anti-Infect. Ther. 14 (2016) 281–283.
[99] E. Kirchner, K.M. Guglielmi, H.M. Strauss, T.S. Dermody, T. Stehle, Structure of reovirus sigma1 in complex with its receptor junctional adhesion molecule-A, PLoS Pathog. 4 (2008), e1000235.
[100] D.M. Reiter, J.M. Frierson, E.E. Halvorson, T. Kobayashi, T.S. Dermody, T. Stehle, Crystal structure of reovirus attachment protein sigma1 in complex with sialylated oligosaccharides, PLoS Pathog. 7 (2011), e1002166.
[101] K. Reiss, J.E. Stencel, Y. Liu, B.S. Blaum, D.M. Reiter, T. Feizi, et al., The GM2 glycan serves as a functional coreceptor for serotype 1 reovirus, PLoS Pathog. 8 (2012), e1003078.
[102] R. Vlasak, W. Luytjes, J. Leider, W. Spaan, P. Palese, The E3 protein of bovine coronavirus is a receptor-destroying enzyme with acetylesterase activity, J. Virol. 62 (1988) 4686–4690.
[103] B. Delmas, J. Gelfi, R. L'Haridon, L.K. Vogel, H. Sjostrom, O. Noren, et al., Aminopeptidase N is a major receptor for the entero-pathogenic coronavirus TGEV, Nature 357 (1992) 417–420.
[104] C. Krempl, B. Schultze, H. Laude, G. Herrler, Point mutations in the S protein connect the sialic acid binding activity with the enteropathogenicity of transmissible gastroenteritis coronavirus, J. Virol. 71 (1997) 3285–3287.
[105] C. Schwegmann-Wessels, G. Herrler, Sialic acids as receptor determinants for coronaviruses, Glycoconj. J. 23 (2006) 51–58.
[106] B. Schultze, H.J. Gross, R. Brossmer, G. Herrler, The S protein of bovine coronavirus is a hemagglutinin recognizing 9-*O*-acetylated sialic acid as a receptor determinant, J. Virol. 65 (1991) 6232–6237.
[107] H. Hofmann, K. Pyrc, L. van der Hoek, M. Geier, B. Berkhout, S. Pohlmann, Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 7988–7993.
[108] J.A. Decaprio, R.L. Garcea, A cornucopia of human polyomaviruses, Nat. Rev. Microbiol. 11 (2013) 264–276.
[109] H.H. Hirsch, P. Randhawa, AST Infectious Diseases Community of Practice, BK polyomavirus in solid organ transplantation, Am. J. Transplant. 13 (Suppl. 4) (2013) 179–188.
[110] H.H. Hirsch, P. Kardas, D. Kranz, C. Leboeuf, The human JC polyomavirus (JCPyV): virological background and clinical implications, APMIS 121 (2013) 685–727.
[111] H. Feng, M. Shuda, Y. Chang, P.S. Moore, Clonal integration of a polyomavirus in human Merkel cell carcinoma, Science (New York, N.Y.) 319 (2008) 1096–1100.

[112] R.C. Liddington, Y. Yan, J. Moulai, R. Sahli, T.L. Benjamin, S.C. Harrison, Structure of simian virus 40 at 3.8-Å resolution, Nature 354 (1991) 278–284.
[113] R.J. Frisque, G.L. Bream, M.T. Cannella, Human polyomavirus JC virus genome, J. Virol. 51 (1984) 458–469.
[114] K.V. Shah, B.N. Fields, D.M. Knipe, P.M. Howley, Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, 1996.
[115] U. Neu, K. Woellner, G. Gauglitz, T. Stehle, Structural basis of GM1 ganglioside recognition by simian virus 40, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 5219–5224.
[116] K.D. Erickson, R.L. Garcea, B. Tsai, Ganglioside GT1b is a putative host cell receptor for the Merkel cell polyomavirus, J. Virol. 83 (2009) 10275–10279.
[117] M. Qian, B. Tsai, Lipids and proteins act in opposing manners to regulate polyomavirus infection, J. Virol. 84 (2010) 9840–9852.
[118] M. Campanero-Rhodes, A. Smith, W. Chai, S. Sonnino, L. Mauri, R. Childs, et al., *N*-glycolyl GM1 ganglioside as a receptor for simian virus 40, J. Virol. 81 (2007) 12846–12858.
[119] C.K. Liu, G. Wei, W.J. Atwood, Infection of glial cells by the human polyomavirus JC is mediated by an N-linked glycoprotein containing terminal alpha(2–6)-linked sialic acids, J. Virol. 72 (1998) 4643–4649.
[120] R. Komagome, H. Sawa, T. Suzuki, Y. Suzuki, S. Tanaka, W.J. Atwood, et al., Oligosaccharides as receptors for JC virus, J. Virol. 76 (2002) 12992–13000.
[121] G.V. Gee, N. Tsomaia, D.F. Mierke, W.J. Atwood, Modeling a sialic acid binding pocket in the external loops of JC virus VP1, J. Biol. Chem. 279 (2004) 49172–49176.
[122] A.S. Dugan, M.L. Gasparovic, W.J. Atwood, Direct correlation between sialic acid binding and infection of cells by two human polyomaviruses (JC virus and BK virus), J. Virol. 82 (2008) 2560–2564.
[123] L. Gorelik, C. Reid, M. Testa, M. Brickelmaier, S. Bossolasco, A. Pazzi, et al., Progressive multifocal leukoencephalopathy (PML) development is associated with mutations in JC virus capsid protein VP1 that change its receptor specificity, J. Infect. Dis. 204 (2011) 103–114.
[124] L.J. Stroh, M.S. Maginnis, B.S. Blaum, C.D. Nelson, U. Neu, G.V. Gee, et al., The greater affinity of JC polyomavirus capsid for alpha2,6-linked lactoseries tetrasaccharide c than for other sialylated glycans is a major determinant of infectivity, J. Virol. 89 (2015) 6364–6375.
[125] K. Hellwig, R. Gold, Progressive multifocal leukoencephalopathy and natalizumab, J. Neurol. 258 (2011) 1920–1928.
[126] E. Kawamoto, S. Nakahashi, T. Okamoto, H. Imai, M. Shimaoka, Anti-integrin therapy for multiple sclerosis, Autoimmune Dis. 2012 (2012) 357101.
[127] E.O. Major, T.A. Yousry, D.B. Clifford, Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned, Lancet Neurol. 17 (2018) 467–480.
[128] Biogen Idec, https://medinfo.biogen.com 2017, Accessed date: 11 April 2017.
[129] S.R. Sunyaev, A. Lugovskoy, K. Simon, L. Gorelik, Adaptive mutations in the JC virus protein capsid are associated with progressive multifocal leukoencephalopathy (PML), PLoS Genet. 5 (2009), e1000368.
[130] S. Delbue, E. Branchetti, S. Bertolacci, E. Tavazzi, E. Marchioni, R. Maserati, et al., JC virus VP1 loop-specific polymorphisms are associated with favorable prognosis for progressive multifocal leukoencephalopathy, J. Neurovirol. 15 (2009) 51–56.
[131] C.E. Reid, H. Li, G. Sur, P. Carmillo, S. Bushnell, R. Tizard, et al., Sequencing and analysis of JC virus DNA from natalizumab-treated PML patients, J. Infect. Dis. 204 (2011) 237–244.
[132] M.S. Maginnis, L.J. Stroh, G.V. Gee, B.A. O'Hara, A. Derdowski, T. Stehle, et al., Progressive multifocal leukoencephalopathy-associated mutations in the JC polyomavirus capsid disrupt lactoseries tetrasaccharide c binding, MBio 4 (2013), e00247-13.
[133] Y. Kondo, M.S. Windrem, L. Zou, D. Chandler-Militello, S.J. Schanz, R.M. Auvergne, et al., Human glial chimeric mice reveal astrocytic dependence of JC virus infection, J. Clin. Invest. 124 (2014) 5323–5336.
[134] U. Ray, P. Cinque, S. Gerevini, V. Longo, A. Lazzarin, S. Schippling, et al., JC polyomavirus mutants escape antibody-mediated neutralization, Sci. Transl. Med. 7 (2015), 306ra151.
[135] S.A. Haley, B.A. O'Hara, C.D. Nelson, F.L. Brittingham, K.J. Henriksen, E.G. Stopa, et al., Human polyomavirus receptor distribution in brain parenchyma contrasts with receptor distribution in kidney and choroid plexus, Am. J. Pathol. 185 (2015) 2246–2258.
[136] M. Sospedra, S. Schippling, S. Yousef, I. Jelcic, S. Bofill-Mas, R. Planas, et al., Treating progressive multifocal leukoencephalopathy with interleukin 7 and vaccination with JC virus capsid protein VP1, Clin. Infect. Dis. 59 (2014) 1588–1592.
[137] Z. Richterova, D. Liebl, M. Horak, Z. Palkova, J. Stokrova, P. Hozak, et al., Caveolae are involved in the trafficking of mouse polyomavirus virions and artificial VP1 pseudocapsids toward cell nuclei, J. Virol. 75 (2001) 10880–10891.
[138] S. Eash, W.J. Atwood, Involvement of cytoskeletal components in BK virus infectious entry, J. Virol. 79 (2005) 11734–11741.
[139] B. Tsai, J. Gilbert, T. Stehle, W. Lencer, T. Benjamin, T. Rapoport, Gangliosides are receptors for murine polyoma virus and SV40, EMBO J. 22 (2003) 4346–4355.
[140] J. Gilbert, T. Benjamin, Uptake pathway of polyomavirus via ganglioside GD1a, J. Virol. 78 (2004) 12259–12267.
[141] E.M. Damm, L. Pelkmans, J. Kartenbeck, A. Mezzacasa, T. Kurzchalia, A. Helenius, Clathrin- and caveolin-1-independent endocytosis: entry of simian virus 40 into cells devoid of caveolae, J. Cell Biol. 168 (2005) 477–488.
[142] H. Ewers, W. Römer, A. Smith, K. Bacia, S. Dmitrieff, W. Chai, et al., GM1 structure determines SV40-induced membrane invagination and infection, Nat. Cell Biol. 12 (2010) 11.
[143] Y. Luo, N. Motamedi, T.G. Magaldi, G.V. Gee, W.J. Atwood, D. Dimaio, Interaction between simian virus 40 major capsid protein VP1 and cell surface ganglioside GM1 triggers vacuole formation, MBio 7 (2016), e00297.
[144] S.D. O'Hara, R.L. Garcea, Murine polyomavirus cell surface receptors activate distinct signaling pathways required for infection, MBio 7 (2016).
[145] B. Assetta, M.S. Maginnis, I. Gracia Ahufinger, S.A. Haley, G.V. Gee, C.D. Nelson, et al., 5-Ht2 receptors facilitate Jc polyomavirus entry, J. Virol. 87 (24) (2013) 13490–13498.
[146] M.T. Pho, A. Ashok, W.J. Atwood, JC virus enters human glial cells by clathrin-dependent receptor-mediated endocytosis, J. Virol. 74 (2000) 2288–2292.
[147] C.B. Coyne, J.M. Bergelson, Virus-induced Abl and Fyn kinase signals permit coxsackievirus entry through epithelial tight junctions, Cell 124 (2006) 119–131.
[148] E. Farahani, H.K. Patra, J.R. Jangamreddy, I. Rashedi, M. Kawalec, R.K. Rao Pariti, et al., Cell adhesion molecules

and their relation to (cancer) cell stemness, Carcinogenesis 35 (2014) 747–759.
[149] P.J. Maddon, A.G. Dalgleish, J.S. Mcdougal, P.R. Clapham, R.A. Weiss, R. Axel, The T4 gene encodes the AIDS virus receptor and is expressed in the immune system and the brain, Cell 47 (1986) 333–348.
[150] H. Tatsuo, N. Ono, K. Tanaka, Y.S.L.A.M. Yanagi, (CDw150) is a cellular receptor for measles virus, Nature 406 (2000) 893–897.
[151] D.E. Staunton, V.J. Merluzzi, R. Rothlein, R. Barton, S.D. Marlin, T.A. Springer, A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses, Cell 56 (1989) 849–853.
[152] C.L. Mendelsohn, E. Wimmer, V.R. Racaniello, Cellular receptor for poliovirus: molecular cloning, nucleotide sequence, and expression of a new member of the immunoglobulin superfamily, Cell 56 (1989) 855–865.
[153] M.S. Maginnis, J.C. Forrest, S.A. Kopecky-Bromberg, S.K. Dickeson, S.A. Santoro, M.M. Zutter, et al., Beta1 integrin mediates internalization of mammalian reovirus, J. Virol. 80 (2006) 2760–2770.
[154] B.S. Coulson, S.L. Londrigan, D.J. Lee, Rotavirus contains integrin ligand sequences and a disintegrin-like domain that are implicated in virus entry into cells, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 5389–5394.
[155] C.A. Guerrero, E. Mendez, S. Zarate, P. Isa, S. Lopez, C.F. Arias, Integrin alpha(v)beta(3) mediates rotavirus cell entry, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 14644–14649.
[156] T.J. Wickham, P. Mathias, D.A. Cheresh, G.R. Nemerow, Integrins alpha v beta 3 and alpha v beta 5 promote adenovirus internalization but not virus attachment, Cell 73 (1993) 309–319.
[157] P.L. Stewart, G.R. Nemerow, Cell integrins: commonly used receptors for diverse viral pathogens, Trends Microbiol. 15 (2007) 500–507.
[158] J.J. Chu, M.L. Ng, Interaction of West Nile virus with alpha v beta 3 integrin mediates virus entry into cells, J. Biol. Chem. 279 (2004) 54533–54541.
[159] G. Cseke, M.S. Maginnis, R.G. Cox, S.J. Tollefson, A.B. Podsiad, D.W. Wright, et al., Integrin alphavbeta1 promotes infection by human metapneumovirus, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 1566–1571.
[160] T. Jackson, W. Blakemore, J.W. Newman, N.J. Knowles, A.P. Mould, M.J. Humphries, et al., Foot-and-mouth disease virus is a ligand for the high-affinity binding conformation of integrin alpha5beta1: influence of the leucine residue within the RGDL motif on selectivity of integrin binding, J. Gen. Virol. 81 (2000) 1383–1391.
[161] T. Jackson, D. Sheppard, M. Denyer, W. Blakemore, A.M. King, The epithelial integrin alphavbeta6 is a receptor for foot-and-mouth disease virus, J. Virol. 74 (2000) 4949–4956.
[162] T. Jackson, A.P. Mould, D. Sheppard, A.M. King, Integrin alphavbeta1 is a receptor for foot-and-mouth disease virus, J. Virol. 76 (2002) 935–941.
[163] T. Jackson, S. Clark, S. Berryman, A. Burman, S. Cambier, D. Mu, et al., Integrin alphavbeta8 functions as a receptor for foot-and-mouth disease virus: role of the beta-chain cytodomain in integrin-mediated infection, J. Virol. 78 (2004) 4533–4540.
[164] A. Kotecha, Q. Wang, X. Dong, S.L. Ilca, M. Ondiviela, R. Zihe, et al., Rules of engagement between alphavbeta6 integrin and foot-and-mouth disease virus, Nat. Commun. 8 (2017) 15408.
[165] T. Gianni, A. Cerretani, R. Dubois, S. Salvioli, S.S. Blystone, F. Rey, et al., Herpes simplex virus glycoproteins H/L bind to cells independently of {alpha}V{beta}3 integrin and inhibit virus entry, and their constitutive expression restricts infection, J. Virol. 84 (2010) 4013–4025.
[166] A.L. Feire, H. Koss, T. Compton, Cellular integrins function as entry receptors for human cytomegalovirus via a highly conserved disintegrin-like domain, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 15470–15475.
[167] T. Gianni, S. Salvioli, L.S. Chesnokova, L.M. Hutt-Fletcher, Campadelli-Fiume G. , Alphavbeta6- and alphavbeta8-integrins serve as interchangeable receptors for HSV gH/gL to promote endocytosis and activation of membrane fusion, PLoS Pathog. 9 (2013), e1003806.
[168] T. Gianni, R. Massaro, G. Campadelli-Fiume, Dissociation of HSV gL from gH by alphavbeta6- or alphavbeta8-integrin promotes gH activation and virus entry, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) E3901–E3910.
[169] J.C. Forrest, J.A. Campbell, P. Schelling, T. Stehle, T.S. Dermody, Structure–function analysis of reovirus binding to junctional adhesion molecule 1. Implications for the mechanism of reovirus attachment, J. Biol. Chem. 278 (2003) 48434–48444.
[170] Q. Li, C. Sodroski, B. Lowey, C.J. Schweitzer, H. Cha, F. Zhang, et al., Hepatitis C virus depends on E-cadherin as an entry factor and regulates its expression in epithelial-to-mesenchymal transition, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 7620–7625.
[171] P. Bork, L. Holm, C. Sander, The immunoglobulin fold. Structural classification, sequence patterns and common core, J. Mol. Biol. 242 (1994) 309–320.
[172] P. Danthi, G.H. Holm, T. Stehle, T.S. Dermody, Reovirus receptors, cell entry, and proapoptotic signaling, Adv. Exp. Med. Biol. 790 (2013) 42–71.
[173] A. Makino, M. Shimojima, T. Miyazawa, K. Kato, Y. Tohya, H. Akashi, Junctional adhesion molecule 1 is a functional receptor for feline calicivirus, J. Virol. 80 (2006) 4482–4490.
[174] Y. Wallez, P. Huber, Endothelial adherens and tight junctions in vascular homeostasis, inflammation and angiogenesis, Biochim. Biophys. Acta 1778 (2008) 794–809.
[175] Y. Liu, A. Nusrat, F.J. Schnell, T.A. Reaves, S. Walsh, M. Pochet, et al., Human junction adhesion molecule regulates tight junction resealing in epithelia, J. Cell Sci. 113 (Pt 13) (2000) 2363–2374.
[176] A.E. Prota, J.A. Campbell, P. Schelling, J.C. Forrest, M.J. Watson, T.R. Peters, et al., Crystal structure of human junctional adhesion molecule 1: implications for reovirus binding, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 5366–5371.
[177] K.M. Guglielmi, E. Kirchner, G.H. Holm, T. Stehle, T.S. Dermody, Reovirus binding determinants in junctional adhesion molecule-A, J. Biol. Chem. 282 (2007) 17930–17940.
[178] J.A. Campbell, P. Schelling, J.D. Wetzel, E.M. Johnson, J.C. Forrest, G.A. Wilson, et al., Junctional adhesion molecule A serves as a receptor for prototype and field-isolate strains of mammalian reovirus, J. Virol. 79 (2005) 7967–7978.
[179] J.D. Chappell, A.E. Prota, T.S. Dermody, T. Stehle, Crystal structure of reovirus attachment protein sigma1 reveals evolutionary relationship to adenovirus fiber, EMBO J. 21 (2002) 1–11.
[180] P. Schelling, K.M. Guglielmi, E. Kirchner, B. Paetzold, T.S. Dermody, T. Stehle, The reovirus sigma1 aspartic acid

sandwich: a trimerization motif poised for conformational change, J. Biol. Chem. 282 (2007) 11582–11589.
[181] E. Stettner, M.H. Dietrich, K. Reiss, T.S. Dermody, T. Stehle, Structure of serotype 1 reovirus attachment protein sigma1 in complex with junctional adhesion molecule A reveals a conserved serotype-independent binding epitope, J. Virol. 89 (2015) 6136–6140.
[182] M.J. van Raaij, A. Mitraki, G. Lavigne, S. Cusack, A triple beta-spiral in the adenovirus fibre shaft reveals a new structural motif for a fibrous protein, Nature 401 (1999) 935–938.
[183] M.J. van Raaij, E. Chouin, H. van der Zandt, J.M. Bergelson, S. Cusack, Dimeric structure of the coxsackievirus and adenovirus receptor D1 domain at 1.7 Å resolution, Structure 8 (2000) 1147–1155.
[184] H.L. Weiner, D. Drayna, D.R. Averill Jr., B.N. Fields, Molecular basis of reovirus virulence: role of the S1 gene, Proc. Natl. Acad. Sci. U. S. A. 74 (1977) 5744–5748.
[185] K.L. Tyler, D.A. Mcphee, B.N. Fields, Distinct pathways of viral spread in the host determined by reovirus S1 gene segment, Science (New York, N.Y.) 233 (1986) 770–774.
[186] J.C. Forrest, T.S. Dermody, Reovirus receptors and pathogenesis, J. Virol. 77 (2003) 9109–9115.
[187] J. Stencel-Baerenwald, K. Reiss, B.S. Blaum, D. Colvin, X.N. Li, T. Abel, et al., Glycan engagement dictates hydrocephalus induction by serotype 1 reovirus, MBio 6 (2015), e02356.
[188] J.M. Frierson, A.J. Pruijssers, J.L. Konopka, D.M. Reiter, T.W. Abel, T. Stehle, et al., Utilization of sialylated glycans as coreceptors enhances the neurovirulence of serotype 3 reovirus, J. Virol. 86 (2012) 13164–13173.
[189] A.A. Antar, J.L. Konopka, J.A. Campbell, R.A. Henry, A.L. Perdigoto, B.D. Carter, et al., Junctional adhesion molecule-A is required for hematogenous dissemination of reovirus, Cell Host Microbe 5 (2009) 59–71.
[190] I.D. Campbell, M.J. Humphries, Integrin structure, activation, and interactions, Cold Spring Harb. Perspect. Biol. 3 (2011).
[191] H.A. Hussein, L.R. Walker, U.M. Abdel-Raouf, S.A. Desouky, A.K. Montasser, S.M. Akula, Beyond RGD: virus interactions with integrins, Arch. Virol. 160 (2015) 2669–2681.
[192] Y. Wei, Y. Zhang, H. Cai, A.M. Mirza, R.M. Iorio, M.E. Peeples, et al., Roles of the putative integrin-binding motif of the human metapneumovirus fusion (f) protein in cell–cell fusion, viral infectivity, and pathogenesis, J. Virol. 88 (2014) 4338–4352.
[193] R.G. Cox, S.B. Livesay, M. Johnson, M.D. Ohi, J.V. Williams, The human metapneumovirus fusion protein mediates entry via an interaction with RGD-binding integrins, J. Virol. 86 (2012) 12148–12160.
[194] A. Chang, C. Masante, U.J. Buchholz, R.E. Dutch, Human metapneumovirus (HMPV) binding and infection are mediated by interactions between the HMPV fusion protein and heparan sulfate, J. Virol. 86 (2012) 3230–3243.
[195] N. Cheshenko, J.B. Trepanier, P.A. Gonzalez, E.A. Eugenin, W.R. Jacobs Jr., B.C. Herold, Herpes simplex virus type 2 glycoprotein H interacts with integrin alphavbeta3 to facilitate viral entry and calcium signaling in human genital tract epithelial cells, J. Virol. 88 (2014) 10026–10038.
[196] K. Schmidt, M. Keller, B.L. Bader, T. Korytar, S. Finke, U. Ziegler, et al., Integrins modulate the infection efficiency of West Nile virus into cells, J. Gen. Virol. 94 (2013) 1723–1733.
[197] G.R. Medigeshi, A.J. Hirsch, D.N. Streblow, J. Nikolich-Zugich, J.A. Nelson, West Nile virus entry requires cholesterol-rich membrane microdomains and is independent of alphavbeta3 integrin, J. Virol. 82 (2008) 5212–5219.
[198] P. Danthi, K.M. Guglielmi, E. Kirchner, B. Mainou, T. Stehle, T.S. Dermody, From touchdown to transcription: the reovirus cell entry pathway, Curr. Top. Microbiol. Immunol. 343 (2010) 91–119.
[199] M.Y. Nakano, K. Boucke, M. Suomalainen, R.P. Stidwill, U.F. Greber, The first step of adenovirus type 2 disassembly occurs at the cell surface, independently of endocytosis and escape to the cytosol, J. Virol. 74 (2000) 7085–7095.
[200] M.Y. Nakano, U.F. Greber, Quantitative microscopy of fluorescent adenovirus entry, J. Struct. Biol. 129 (2000) 57–68.
[201] S. Lindert, M. Silvestry, T.M. Mullen, G.R. Nemerow, P.L. Stewart, Cryo-electron microscopy structure of an adenovirus–integrin complex indicates conformational changes in both penton base and integrin, J. Virol. 83 (2009) 11491–11501.
[202] E. Li, D. Stupack, R. Klemke, D.A. Cheresh, G.R. Nemerow, Adenovirus endocytosis via alpha(v) integrins requires phosphoinositide-3-OH kinase, J. Virol. 72 (1998) 2055–2061.
[203] E. Li, D. Stupack, G.M. Bokoch, G.R. Nemerow, Adenovirus endocytosis requires actin cytoskeleton reorganization mediated by Rho family GTPases, J. Virol. 72 (1998) 8806–8812.
[204] O. Meier, K. Boucke, S.V. Hammer, S. Keller, R.P. Stidwill, S. Hemmi, et al., Adenovirus triggers macropinocytosis and endosomal leakage together with its clathrin-mediated uptake, J. Cell Biol. 158 (2002) 1119–1131.
[205] A.S. Kondratowicz, N.J. Lennemann, P.L. Sinn, R.A. Davey, C.L. Hunt, S. Moller-Tank, et al., T-cell immunoglobulin and mucin domain 1 (TIM-1) is a receptor for Zaire Ebolavirus and Lake Victoria Marburgvirus, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 8426–8431.
[206] S. Bhattacharyya, A. Zagorska, E.D. Lew, B. Shrestha, C.V. Rothlin, J. Naughton, et al., Enveloped viruses disable innate immune responses in dendritic cells by direct activation of TAM receptors, Cell Host Microbe 14 (2013) 136–147.
[207] R. Hamel, O. Dejarnac, S. Wichit, P. Ekchariyawat, A. Neyret, N. Luplertlop, et al., Biology of Zika virus infection in human skin cells, J. Virol. 89 (2015) 8880–8896.
[208] L. Meertens, A. Labeau, O. Dejarnac, S. Cipriani, L. Sinigaglia, L. Bonnet-Madin, et al., Axl mediates ZIKA virus entry in human glial cells and modulates innate immune responses, Cell Rep. 18 (2017) 324–333.
[209] S. Moller-Tank, A.S. Kondratowicz, R.A. Davey, P.D. Rennert, W. Maury, Role of the phosphatidylserine receptor TIM-1 in enveloped-virus entry, J. Virol. 87 (2013) 8327–8341.
[210] J. Mercer, A. Helenius, Vaccinia virus uses macropinocytosis and apoptotic mimicry to enter host cells, Science (New York, N.Y.) 320 (2008) 531–535.
[211] P. Vanlandschoot, G. Leroux-Roels, Viral apoptotic mimicry: an immune evasion strategy developed by the hepatitis B virus? Trends Immunol. 24 (2003) 144–147.
[212] C.L. Hunt, A.A. Kolokoltsov, R.A. Davey, W. Maury, The Tyro3 receptor kinase Axl enhances macropinocytosis of Zaire ebolavirus, J. Virol. 85 (2011) 334–347.
[213] M. Shimojima, A. Takada, H. Ebihara, G. Neumann, K. Fujioka, T. Irimura, et al., Tyro3 family-mediated cell entry of Ebola and Marburg viruses, J. Virol. 80 (2006) 10109–10116.
[214] A. Nanbo, J. Maruyama, M. Imai, M. Ujie, Y. Fujioka, S. Nishide, et al., Ebola virus requires a host scramblase for

externalization of phosphatidylserine on the surface of viral particles, PLoS Pathog. 14 (2018), e1006848.
[215] P. Simmonds, P. Becher, J. Bukh, E.A. Gould, G. Meyers, T. Monath, et al., ICTV virus taxonomy profile: Flaviviridae, J. Gen. Virol. 98 (2017) 2–3.
[216] F.A. Rey, K. Stiasny, M.C. Vaney, M. Dellarole, F.X. Heinz, The bright and the dark side of human antibody responses to flaviviruses: lessons for vaccine design, EMBO Rep. 19 (2018) 206–224.
[217] WHO, West Nile virus, 2018.
[218] CDC, Zika Virus Overview, 2018.
[219] C. Guo, Z. Zhou, Z. Wen, Y. Liu, C. Zeng, D. Xiao, et al., Global epidemiology of dengue outbreaks in 1990-2015: a systematic review and meta-analysis, Front. Cell. Infect. Microbiol. 7 (2017) 317.
[220] Z.Y. Wang, Z. Wang, Z.D. Zhen, K.H. Feng, J. Guo, N. Gao, et al., Axl is not an indispensable factor for Zika virus infection in mice, J. Gen. Virol. 98 (2017) 2061–2068.
[221] M.F. Wells, M.R. Salick, O. Wiskow, D.J. Ho, K.A. Worringer, R.J. Ihry, et al., Genetic ablation of AXL does not protect human neural progenitor cells and cerebral organoids from Zika virus infection, Cell Stem Cell 19 (2016) 703–708.
[222] J. Chen, Y.F. Yang, Y. Yang, P. Zou, J. Chen, Y. He, et al., AXL promotes Zika virus infection in astrocytes by antagonizing type I interferon signalling, Nat. Microbiol. 3 (2018) 302–309.
[223] A.S. Richard, B.S. Shim, Y.C. Kwon, R. Zhang, Y. Otsuka, K. Schmitt, et al., AXL-dependent infection of human fetal endothelial cells distinguishes Zika virus from other pathogenic flaviviruses, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 2024–2029.
[224] C.B. Wilen, J.C. Tilton, R.W. Doms, Molecular mechanisms of HIV entry, Adv. Exp. Med. Biol. 726 (2012) 223–242.
[225] P.J. Maddon, J.S. Mcdougal, P.R. Clapham, A.G. Dalgleish, S. Jamal, R.A. Weiss, et al., HIV infection does not require endocytosis of its receptor, CD4, Cell 54 (1988) 865–874.
[226] N.R. Landau, M. Warton, D.R. Littman, The envelope glycoprotein of the human immunodeficiency virus binds to the immunoglobulin-like domain of CD4, Nature 334 (1988) 159–162.
[227] A.C. Saphire, M.D. Bobardt, Z. Zhang, G. David, P.A. Gallay, Syndecans serve as attachment receptors for human immunodeficiency virus type 1 on macrophages, J. Virol. 75 (2001) 9187–9200.
[228] J. Arthos, C. Cicala, E. Martinelli, K. Macleod, D. Van Ryk, D. Wei, et al., HIV-1 envelope protein binds to and signals through integrin alpha4beta7, the gut mucosal homing receptor for peripheral T cell, Nat. Immunol. 9 (2008) 301–309.
[229] T.B. Geijtenbeek, D.S. Kwon, R. Torensma, S.J. van Vliet, G.C. van Duijnhoven, J. Middel, et al., DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells, Cell 100 (2000) 587–597.
[230] G. Alkhatib, The biology of CCR5 and CXCR4, Curr. Opin. HIV AIDS 4 (2009) 96–103.
[231] C.B. Wilen, J.C. Tilton, R.W. Doms, HIV: cell binding and entry, Cold Spring Harb. Perspect. Med. 2 (2012).
[232] B.A. Mainou, A.W. Ashbrook, E.C. Smith, D.C. Dorset, M.R. Denison, T.S. Dermody, Serotonin receptor agonist 5-nonyloxytryptamine alters the kinetics of reovirus cell entry, J. Virol. 89 (2015) 8701–8712.
[233] H. Cheng, C.M. Lear-Rooney, L. Johansen, E. Varhegyi, Z.W. Chen, G.G. Olinger, et al., Inhibition of Ebola and Marburg virus entry by G protein-coupled receptor antagonists, J. Virol. 89 (2015) 9932–9938.
[234] G.J. Stewart, L.J. Ashton, R.A. Biti, R.A. Ffrench, B.H. Bennetts, N.R. Newcombe, et al., Increased frequency of CCR-5 delta 32 heterozygotes among long-term non-progressors with HIV-1 infection. The Australian Long-Term Non-Progressor Study Group, AIDS (London, England) 11 (1997) 1833–1838.
[235] G.G. Xu, J. Guo, Y. Wu, Chemokine receptor CCR5 antagonist maraviroc: medicinal chemistry and clinical applications, Curr. Top. Med. Chem. 14 (2014) 1504–1514.
[236] P. Dorr, M. Westby, S. Dobbs, P. Griffin, B. Irvine, M. Macartney, et al., Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity, Antimicrob. Agents Chemother. 49 (2005) 4721–4732.
[237] S.M. Woollard, G.D. Kanmogne, Maraviroc: a review of its use in HIV infection and beyond, Drug Des. Dev. Ther. 9 (2015) 5447–5468.
[238] M.R. Lopez-Huertas, L. Jimenez-Tormo, N. Madrid-Elena, C. Gutierrez, S. Rodriguez-Mora, M. Coiras, et al., The CCR5-antagonist Maraviroc reverses HIV-1 latency in vitro alone or in combination with the PKC-agonist Bryostatin-1, Sci. Rep. 7 (2017) 2385.
[239] A. Kumar, J.H. Kim, P. Ranjan, M.G. Metcalfe, W. Cao, M. Mishina, et al., Influenza virus exploits tunneling nanotubes for cell-to-cell spread, Sci. Rep. 7 (2017) 40360.
[240] J. Ariazi, A. Benowitz, V. De Biasi, M.L. Den Boer, S. Cherqui, H. Cui, et al., Tunneling nanotubes and gap junctions-their role in long-range intercellular communication during development, health, and disease conditions, Front. Mol. Neurosci. 10 (2017) 333.
[241] G. Okafo, L. Prevedel, E. Eugenin, Tunneling nanotubes (TNT) mediate long-range gap junctional communication: implications for HIV cell to cell spread, Sci. Rep. 7 (2017) 16660.
[242] P.J. Gaskill, H.H. Yano, G.V. Kalpana, J.A. Javitch, J.W. Berman, Dopamine receptor activation increases HIV entry into primary human macrophages, PLoS One 9 (2014), e108232.
[243] L. Dai, J. Song, X. Lu, Y.Q. Deng, A.M. Musyoki, H. Cheng, et al., Structures of the Zika virus envelope protein and its complex with a flavivirus broadly protective antibody, Cell Host Microbe 19 (2016) 696–704.
[244] M.S. Kariolis, Y.R. Miao, D.S. Jones II, S. Kapur, I.I. Mathews, A.J. Giaccia, et al., An engineered Axl 'decoy receptor' effectively silences the Gas6–Axl signaling axis, Nat. Chem. Biol. 10 (2014) 977–983.
[245] M.S. Kariolis, Y.R. Miao, A. Diep, S.E. Nash, M.M. Olcina, D. Jiang, et al., Inhibition of the GAS6/AXL pathway augments the efficacy of chemotherapies, J. Clin. Invest. 127 (2017) 183–198.