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REVIEW

Beyond RGD: virus interactions with integrins

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Abstract Viruses successfully infect host cells by initially binding to the surfaces of the cells, followed by an intricate entry process. As multifunctional heterodimeric cell-surface receptor molecules, integrins have been shown to usefully serve as entry receptors for a plethora of viruses. However, the exact role(s) of integrins in viral pathogen internalization has yet to be elaborately described. Notably, several viruses harbor integrin-recognition motifs displayed on viral envelope/capsid-associated proteins. The most common of these motifs is the minimal peptide sequence for binding integrins, RGD (Arg-Gly-Asp), which is known for its role in virus infection via its ability to interact with over half of the more than 20 known integrins. Not all virus-integrin interactions are RGD-dependent, however. Non-RGD-binding integrins have also been shown to effectively promote virus entry and infection as well. Such virus-integrin binding is shown to facilitate adhesion, cytoskeleton rearrangement, integrin activation, and increased intracellular signaling. Also, we have attempted to discuss the role of carbohydrate moieties in virus interactions with receptor-like host cell surface integrins that drive the process of internalization. As much as possible, this article examines the published literature regarding the role of integrins in terms of virus infection and virus-encoded glycosylated proteins that mediate interactions with integrins, and it explores the idea of targeting these receptors as a therapeutic treatment option.

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Introduction

Viruses may be small in size, but they carry enough genetic material that they are capable of inflicting some of the deadliest diseases in the world. If not for their ability to enter host cells and efficiently impair them, we would not even talk about them. An efficient pathogen is one that has evolved a robust entry mechanism for delivery of genetic material into different target host cells, which is critical for replication and sustenance. Over the years, viruses as obligate parasites have evolved successful ways to colonize host cells, using complicated but well-orchestrated mechanisms to enter cells.

The whole process of virus entry—otherwise referred to as internalization—begins with the virus binding to target cells. Binding to cells is a reversible process that does not ensure virus entry. Virus binding or attachment only ensures viral proximity to cells. However, this process is the most essential step that kick-starts the whole cascade of events, resulting in the eventual internalization of the virus. Several viruses utilize different glycosaminoglycans expressed on the target cells as binding receptors. Glycosaminoglycans serve as good receptor molecules that promote binding, as they are expressed ubiquitously in eukaryotic cells. Some of the most common binding receptors are heparan sulfate (HS) and chondroitin sulfate [4, 82, 99, 143, 167]. Virus binding to such receptors brings them closer to cells and provides the opportunity to interact with other receptor molecules that promote the actual internalization process. Several scientists have

hypothesized that the initial step of virus binding to cells also induces conformational changes to the glycoproteins expressed on the target cells that are critical for the virus to interact with other receptor molecules, thus promoting internalization.

The actual virus entry is complicated to the extent that a single virus may utilize different receptors to efficiently enter different target cells [6, 19]. Viruses have evolved such mechanisms to be effective pathogens. Such variations in the entry mechanisms dictate the actual entry route. For example, Epstein-Barr virus (EBV) enters lymphoblastoid cells by fusion but enters B cells via endocytosis [112]. Integrins are a family of receptor molecules that serve as entry receptors for a variety of different viruses, including foot-and-mouth disease virus (FMDV) [97], Kaposi's sarcoma-associated herpesvirus (KSHV) [5], herpes simplex virus-2 (HSV-2) [31], adenovirus [168], human papillomavirus-16 (HPV-16) [3], reovirus [40], and others. Our understanding of the role of integrins in promoting virus entry is still not complete. In this review, we have attempted to elaborate on the role of integrins in virus internalization.

What are integrins?

Integrins play an important role in regulating a variety of cellular functions, including cell adhesion, cell migration, and critical signaling processes. This is possible because of their ability to interact with various ligands, including extracellular matrix glycoproteins (i.e., collagens, fibronectins, laminins, etc.) and cellular receptors (i.e., vascular cell adhesion molecule-1 and intercellular cell adhesion molecules) [85, 86, 124]. Discovered over twenty years ago, integrins are a large family of transmembrane glycoproteins found in a variety of organisms ranging from sponges, corals, nematodes, and echinoderms to mammals [20].

There are about 24 integrins that have been identified. These heterodimeric receptor molecules result from different pairings among 18 α and 8 β subunits [86]. Each integrin subunit has three domains: an extracellular, transmembrane, and cytoplasmic domain. The extracellular domain is the largest part, ranging from 80 to 150 kDa, while the cytoplasmic domain is a short and largely unstructured domain of 10-70 amino acid (aa) residues, with the exception of the b4 subunit, which contains >1,000 aa residues [148]. The transmembrane domains of integrins are single-spanning structures comprised of 25-29 aa residues that form α-helical coiled coils that exist as either homo- or heterodimers [2].

High-resolution X-ray crystallography structural data are available for the extracellular domains of integrins [9, 98, 183], but no high-resolution experimental X-ray crystal structures are available for the transmembrane or cytoplasmic domain of any integrin heterodimer. Much of the structural data of the transmembrane and cytoplasmic domains are based purely on NMR analysis. Integrins can shift between high- and low-affinity conformations for ligand binding to transduce intracellular signals following ligand binding. In the inactive state, the extracellular domain of integrins is not bound to ligands and exists in a bent conformation. However, signals from the cell induce conformational changes that expose the external ligand-binding site, where ligands bind and transmit the signals from outside to inside the cell [148].

Although some integrins can bind their ligands in a resting state, there are other integrins whose binding to their ligand requires activation through alterations in the intracellular domains by signaling events, which subsequently lead to transmission of signals from inside to outside of the cell; this is commonly referred to as inside-out signaling [37]. Ligand binding to extracellular domains of integrins leads to activation of integrins and subsequent transmission of cellular signals from outside to inside of the cell, which is known as outside-in signaling [182]. These intracellular signals are very important for cell growth, differentiation, and apoptosis. Additionally, intracellular signals lead to formation of the focal adhesion complex, which is a large and dynamic multi-protein complex that includes a vast number of intracellular proteins [185].

Along with proteoglycans, integrins form the major adhesion receptors for extracellular cellular matrix (ECM) proteins, making them important for signaling events that determine cell fate [94]. Cellular signaling processes depend on the pattern of expression and the composition of integrins, which determine the ECM type a cell can bind and initiate downstream signaling events [78]. Integrins provide a connection between the ECM proteins and the actin cytoskeleton that is crucial for regulating cytoskeletal organization and intracellular signaling pathways, all of which are a necessity for cell survival, proliferation, shape, attachment, migration, and angiogenesis [148].

As adhesion molecules, integrins mediate cell-to-cell, cell-to-ECM, and cell-to-pathogen interactions, and such adhesion is regulated through the inside-out signaling process. Integrin-induced adhesion is very important in the regulation of the immune system during leukocyte trafficking, migration, and phagocytosis [108]. Adhesion of integrins to a solid surface is the first step in cell migration and motility. The vital role of integrins in cell migration makes them essential for many important biological events, including embryonic development [58, 189], inflammatory responses [50, 55, 101], wound healing [7, 24], and tumor metastasis [81]. There are many pathogens, including

viruses [45, 89, 146] and bacteria [76, 80], that have the ability to use integrins with different mechanisms for invading cells. Through regulation of several cell functions, integrins have a role in human disease. For example, tumors, cancer, and immunodeficiency disorders are all associated with altered integrin-mediated adhesion and migration [84].

The hallmark of tumor development is cell attachment, migration, and proliferation; all of which are regulated by integrin-based cellular signaling [71, 113, 170]. Expression of particular integrins, including α6β4, α6β1, αVβ5, α2β1 and α3β1, on tumor cells in the context of activated cytokine receptors or growth factor receptors leads to increased disease progression and severity [42]. Integrins integrate the extracellular and intracellular environments by binding to ligands outside the cell and cytoskeletal components and signaling molecules inside the cell [108]. The role of integrins in cancer initiation and progression makes them targets for several therapeutic agents in clinical trials of cancer therapy.

What are the roles of integrins in virus entry of cells?

Integrins have been exploited by many pathogens, including bacteria and viruses to infect cells. Penetration of the host-cell plasma membrane is a crucial step for a successful virus infection [178]. To invade the host cell, several animal viruses physically interact with integrins to infect cells. There are many studies that demonstrate the critical role of membrane rafts in viral entry and infection [22, 153]. Interestingly, many integrins used by viruses for binding and internalization are localized to and associated with membrane rafts, which consolidate the role of integrin in virus internalization and infection [30, 70, 116, 153]. A list of viruses and the manner by which they utilize integrins to infect cells is provided in Table 1.

RGD-binding integrins and their effect on virus infection of cells

Many viruses, including adenoviruses and herpesviruses, have an RGD (Arg-Gly-Asp) tripeptide motif displayed on their viral envelope glycoproteins. RGD is the minimal peptide sequence for binding integrins. As an integrin-recognition motif, RGD plays an important role in virus infection by binding one or different combinations of several integrins, which include αVβ1, αVβ3, αVβ5, α5β1, αVβ6, αVβ8, and αIIbβ3 [28, 127, 132, 140]. RGD binding to these integrins activates cellular signals such as phosphatidylinositol-3-kinase (PI-3K) and mitogen-activate protein kinase (MAPK) pathways, which are critical for supporting virus infection of cells [5, 106].

Many serotypes of adenovirus use RGD-binding integrins to stimulate endocytosis and thereby promote virus entry [41, 106, 177]. Binding of the RGD motif on the adenovirus penton base capsid protein to integrins initiates virus internalization by stimulating endocytosis via clathrin-coated vesicles [11, 104, 150]. Philpott and colleagues demonstrated that blocking adenovirus binding to integrins using an RGD peptide resulted in a 2- to 3-fold reduction in viral DNA intake [123]. Likewise, studies by Shayakhmetov and colleagues revealed that the deletion of the RGD motif in the penton base did not affect virus attachment but significantly reduced the rate of virus internalization, specifically at the step that involves endosomal escape [140].

Several members of the family *Herpesviridae* interact with integrins in an RGD-dependent manner. For example, herpes simplex virus type 1 (HSV-1) envelope-associated gH interacts with αVβ3, which is critical for virus entry of cells [122]. KSHV or human herpesvirus 8 (HHV-8) interacts with a variety of cellular integrins, including α3β1, αVβ3, and αVβ5, and activates focal adhesion kinase (FAK), Src, PI-3K, Rho GTPases, and diaphanous 2 (Dia2)-associated signaling, which is a necessity for the internalization of the virus [28, 117]. The ability of KSHV to interact with integrins is mediated by the RGD motif of envelope-associated gB [5, 61, 74]. Interestingly, the RGD motif of gB is also required to mediate attachment of cells to the endothelium [44].

RGD-binding integrins are also important for other viruses. For example, the interaction between RGD of capsid protein VP1 of coxsackievirus A9 and αVβ3 is essential for virus binding and entry into cells [77, 130, 131]. There are also other studies that demonstrate that a high-affinity interaction between RGD of coxsackievirus A9 and αVβ6 (compared to αVβ3) is important for cell entry and virus uncoating [77, 138, 180]. Notably, the RGD sequence is highly conserved in the VP1 protein of FMDV and mediates virus attachment to integrins, and thus internalization [47]. Synthetic RGD peptides have been shown to block FMDV attachment in a dose-dependent manner [57, 88, 119]. HIV-1 Tat protein interacts with RGD-binding αVβ5, αVβ3, and α5β1 and initiates the integrin endocytic pathway, which is essential for entry of the virus [13, 160, 173]. HIV-1 Tat protein's interaction with RGD-binding integrin(s) is important for adhesion of target cells [12, 114]. Interactions of the more deadly Ebola virus with α5β1 is deemed critical for modulating infection of fibroblasts [135]. Thus, RGD interactions between viral proteins and integrins seem to regulate not only virus infection of cells but also the associated pathogenesis.

Table 1 Integrins used by different viruses and their role in virus infection

Virus	Integrins	Role of integrins	References
Human adenovirus type 2/5	αvβ3, αvβ5, αvβ1, α5β1, αLβ2, αMβ2	Cell entry, endosome escape	[32, 68, 151, 177, 181]
Human cytomegalovirus (HCMV)	α2β1, α6β1, αvβ3	Cell entry	[53]
Kaposi's sarcoma-associated herpesvirus (KSHV)	α3β1, αVβ3, αVβ5, α9β1	Cell entry	[5, 28, 169, 174]
Epstein-Barr virus (EBV)	αVβ3, αVβ5, α5β1	Cell entry	[166]
Human immunodeficiency virus 1 (HIV-1)	α4β7, αVβ5, αVβ3, α5β1	Cell attachment	[10, 35, 114, 173]
HPS-associated hantaviruses NY-1 and Sin Nombre virus (SNV)	αVβ3, αIIbβ3	Cell attachment, entry	[62, 127]
Rotavirus	α4β1, α4β7, α2β1, αVβ3, αxβ2	Cell attachment, entry	[66, 67, 69, 107]
Echovirus types 1	α2β1, αVβ3	Cell attachment, entry	[49, 92, 162]
Echovirus types 9	αVβ3	Cell attachment, entry	[150]
Foot-and-mouth disease virus (FMDV)	α5β1, αVβ3, αVβ6, αVβ8, αVβ1	Cell attachment, entry	[88, 100, 176]
Coxsackievirus A9	αVβ3, αVβ6	Cell attachment, entry	[129, 138, 150, 164]
Murine polyomavirus	α4β1	Cell entry	[25]
Vaccinia virus	β1	Cell entry	[87]
West Nile virus	αvβ3, αvβ1	Cell entry	[33, 134]
Simian virus 40	α2β1	Cell attachment, entry	[149]
Ross River (RR) virus	α1β1	Cell attachment, entry	[96]
Human papillomavirus	α6β4	Cell attachment	[37, 184]
Ebola virus	α5β1	Cell entry	[135]

Do viruses utilize non-RGD-binding integrins to enter cells?

Not all integrins recognize and interact with the conserved RGD motif of viral proteins. There are multiple other non-RGD-binding integrins that drive virus entry and infection [105, 150]. Some of the non-RGD-binding integrins that promote entry and infection of HCMV [54], KSHV [174], simian virus 40 (SV40) [149], and Ross River virus (RRV) [96] are α1β1, α2β1, α4β1, α6β1, α9β1 and αxβ2.

α1β1 and α2β1 are collagen receptors that are utilized by viruses for cell entry and infection. RRV is an alphavirus that is endemic to Australia and New Guinea and is etiologically associated with epidemic polyarthritis [75, 115]. RRV interacts with α1β1 to infect target cells [60, 96]. Infection of RRV has been shown to be blocked by function-blocking antibodies to α1β1, soluble α1β1 integrin, or peptides representing the α1β1 integrin-binding site on collagen IV [96]. Rotavirus utilizes different non-RGD binding domains to interact with integrins. (i) The Tyr-Gly-Leu (YGL) sequence of the rotavirus spike protein, VP4, interacts with α4β1 and α4β7 and helps the rotavirus to bind and enter cells [66], and (ii) the GPR sequence in the rotavirus spike protein VP7 interacts with αxβ2 and helps the rotavirus to enter cells [64, 65]. Integrins also have a critical role to play in rotavirus pathogenesis. Integrin α1β1 and α2β1 are important receptors for enterotoxin function and pathogenesis through their interactions with rotavirus NSP4, which eventually results in diarrhea [137].

Human echovirus 1 (EV1), which belongs to the family *Picornaviridae* (a family of RNA viruses) is implicated in many human diseases, including meningoencephalitis and carditis. EV1 successfully infects cells by interacting with α2β1 integrin in an RGD-independent manner. In fact, α2β1 clustering on the surface of cells is the determining factor that defines the success rate of the EV1-mediated signaling pathway and virus infection of cells [15, 92, 186]. Also, HIV-1 interacts with the non-RGD-binding integrin α4β7 via gp120, which is critical for efficient cell-to-cell spread of the virus [10, 35, 72]. More interestingly, Cicala et al. hypothesize that gp120-α4β7 interactions play an important role in the very early events following sexual transmission of HIV and may have important implications in the design of vaccine strategies for the prevention of acquisition of HIV infection [36]. Stergiou et al., determined that α2β1 plays a crucial role in modulating SV40-induced cellular signaling and infection [149]. There is also evidence that indicates a role for α2β1 integrin in promoting human papillomavirus (HPV)-induced squamous epithelial dysplasia [161].

Apart from the traditional RGD motif, herpesvirus glycoprotein B (gB) possesses a disintegrin-like domain (DLD) [53, 54]. A role for DLD in HCMV and KSHV entry and infection has been described recently. HCMV interacts with α2β1 and α6β1 [53], and KSHV interacts with α9β1 [174] via the DLD contained within gB to successfully enter cells.

The minimum component of the disintegrin module required for integrin engagement is the 12- to 13-amino-acid disintegrin loop, for which a consensus sequence has been described: RX_6DLXXF [48]. In the case of KSHV gB, the DLD sequence is $RX_{5-7}D/ELXXF/LX_5C$ (aa 66-85; with a conservative D to **E** substitution). Overall, viruses seem to use non-RGD- and RGD-binding integrins to a comparable extent as a means of binding and entering cells.

Comparison of the roles of RGD- versus non-RGD-binding integrins in assisting virus infection of cells

Integrins play a crucial role in cellular function through interactions with a variety of ligands. Integrins are ligand specific and can be grouped into four major groups: laminin-binding integrins (α1β1, α2β1, α3β1, α6β1, α7β1, and α6β4), collagen-binding integrins (α1β1, α2β1, α3β1, α10β1, and α11β1), leukocyte integrins (αLβ2, αMβ2, αXβ2, and αDβ2), and RGD-recognizing integrins (α5β1, αVβ1, αVβ3, αVβ5, αVβ6, αVβ8, and αIIbβ3) [155]. Interestingly, RGD and non-RGD-binding integrins aid equally in the internalization of viruses (Table 2).

The key cellular components that are altered by interactions of integrin with viruses

Virus-integrin binding induces changes in the quaternary structure of the integrin resulting in clustering of subunits, which increases virus affinity, cytoskeletal rearrangement, and subsequent virus internalization [150]. These conformational changes are critical for integrins to achieve outside-in and inside-out signaling necessary for various cellular functions, including cytoskeleton activation, endocytosis, gene expression, cell motility, attachment, cell cycle, cell growth, apoptosis, and differentiation [28, 108]. On the other hand, interactions of viruses with cellular integrins induce conformational changes in the viral surface proteins, helping to expose the essential domains required for virus entry into a host cell [107].

Through integrin activation, viruses can induce FAK phosphorylation which is followed by the activation of several focal adhesion-associated signal molecules, including Src, PI-3K, Rho GTPases (RhoA, Rac, and Cdc42), Dia2, and other effector molecules, such as AKT, ezrin, protein kinase C (PKC), MAPK (MEK, ERK1/2), NF-kB, and p38MAPK [5, 28]. Focal adhesion and associated molecules play critical roles in mediating the internalization of viral DNA into target cells [1, 95].

Src is one of the cellular components that is activated immediately upon activation of FAK by virus-integrin interactions. Src-mediated tyrosine phosphorylation of clathrin regulates clathrin translocation to the plasma membrane, which is important for interactions of clathrin with a number of other essential proteins, including AP2, Eps15, and dynamin. Src-mediated tyrosine phosphorylation also plays a role in endocytosis by releasing the internalized endocytic vesicles and initiating the assembly of the plasma-membrane-associated Ras activation complex [21, 26]. PI-3K and Ras are directly responsible for activating Rho and Rab GTPases. These GTPases, along with the activated ERK1/2, are critical for the microtubule and microfilament reorganization that determines the formation of various types of endocytic vesicles and their movements, as well as acting as a force to drive the virus inside and closer to the nuclear membrane [28].

Many viruses use microtubules and cytoplasmic dynein for nuclear targeting [43]. Virus-induced activity of Rho GTPases such as RhoA and Rac1 increase the efficiency of viral trafficking along microtubules to the nucleus. Thus, inactivation of these Rho proteins affects the stability of microtubules, thereby limiting the delivery of viral nucleic acids into the nucleus [110]. Ezrin is the best-studied member of the downstream effector molecules induced by Rho GTPases, and it is a critical element for cross-linking the actin cytoskeleton with the plasma membrane and inducing the morphological changes that are commonly observed in cells being infected by viruses and other pathogens [139]. Rac, Rho, Cdc42, and Rab5 also act as switching molecules that are essential for internalization of any pathogen due to their ability to modulate actin dynamics, formation of endocytic vesicles and their fission,

Table 2 Functions of RGD and non-RGD binding integrins

Class	Integrin	Functions in virus infection	References
RGD binding	αVβ1 αVβ3 αVβ5 α5 β1 αVβ6 αVβ8 αIIbβ3 αMβ2 αLβ2 α3β1	Cell attachment, entry, signaling, and endosome escape	[5, 62, 83, 100, 107, 127, 140, 150, 176]
Non-RGD binding	α1β1 α2β1 α4β1 α6β1 α9β1 αxβ2 α6β4	Cell attachment, entry, signaling, and endosome escape	[10, 25, 28, 32, 35, 37, 53, 68, 96, 169, 173]

cytoskeletal transport, endosome movement, fusion of endocytic vesicles, and recycling [1, 27, 139].

Adenoviruses, echoviruses, FMDV, parechoviruses, parvoviruses, rotaviruses, KSHV, hantaviruses, and others enter target cells via endocytosis by physically interacting with integrins, resulting in the activation of the FAK–Src–PI-3K signaling pathway [111, 139, 179]. PI-3K-induction in a integrin-FAK-Src-dependent manner plays an important role in virus entry and infection via activation of the Rho family of GTPases and ezrin, and mediates actin cytoskeleton reorganization. Interestingly, these events initiate a cascade of intracellular signals that eventually activate the mitogen-activated protein kinase (MAPK) pathways, which are very important in modulating a variety of cellular processes, including proliferation, differentiation, survival, and apoptosis [117, 163]. In terms of cellular machinery, actin cytoskeleton reorganization is the crux that supports integrin-associated signaling-induced virus entry. Apart from working as a structural platform stabilizing cellular signaling molecules, actin provides mechanical force for endosome formation and endocytic vesicle propulsion [139, 157]. Microtubules and microfilaments along with other cytoskeletal elements play an important role in controlling the intracellular movement of many viruses [39, 102, 103, 118, 126].

A key role for carbohydrate moieties on the cell surface in virus-integrin interactions

Successful virus infection involves multiple steps, which include initial binding to the cell surface, internalization, replication, and egress. In the initial step of virus infection, these versatile infectious agents can bind several different cellular surface molecules, such as proteins, lipids, and carbohydrates. These molecules may function in mediating attachment (i.e., concentrating virus on the cell surface) or serve as receptors or co-receptors facilitating viral endocytosis, conformational changes, and the initiation of signaling pathways associated with infection [121, 158].

In addition to the protein receptor, which is generally dubbed the 'principal' receptor, the carbohydrate moiety of host-cell membrane proteoglycans, glycosphingolipids, and glycoproteins also serve as viral receptors. For instance, HIV-1, via its glycoprotein subunits gp41 and gp120, attached to cell-surface carbohydrates (i.e., glycosphingolipids, galactosylceramide, and heparan sulfate proteoglycans [HSPGs]) as a means of promoting actual virus binding to cells [8, 51, 171]. Similarly, several human herpesviruses, including HSV [147], KSHV [4], and CMV [93], make their initial contact with cells by binding to cell-surface HSPGs.

Expressing many glycan-binding proteins [46], viruses have been shown to bind host-cell carbohydrate attachment receptors in what is considered a charge-transfer-based lectin-sugar interaction [18]. Lectins are glycoproteins that bind sugar with high specificity [8], and these lectin-glycoconjugate interactions have been shown to involve hydrogen bonding, van der Waals interactions, and hydrophobic binding [8, 159]. Many enveloped and nonenveloped viruses have multiple lectin sites on their multimeric surface proteins; the apparent lectin clustering allows for potentially numerous interactions with cellular surface receptors and notably higher-affinity binding to the oligosaccharide attachment receptors compared to monomeric endogenous lectins [18, 79, 142, 158, 175]. The influenza virus haemagglutinin glycoprotein is one example of a common viral lectin-binding protein that binds to sialyloligosaccharide carbohydrate receptors on epithelial cell surfaces with high affinity [144, 172, 187]. Similarly, sialyloligosaccharide receptors serve as a means of cell attachment for other viruses, including human JC virus, Sendai virus, and sialyloligosaccharide-dependent strains of rotavirus and reovirus [18]. Specifically, C-type lectins are associated with HIV, SARS coronavirus, and measles virus infections. Likewise, S-type, P-type and I-type lectins are important for promoting infection of HIV, HTLV-1,VZV, and porcine reproductive and respiratory syndrome virus (PRRSV) [38, 63, 133].

In general, binding of viruses to carbohydrate moieties on the surface of cells is the key step that induces conformational changes in the viral structure that are critical for interactions with entry-promoting receptors such as integrins. Blocking this step of virus interactions with carbohydrate moieties impairs viral entry via integrins [4]. A list of viruses that utilize carbohydrate moieties to promote virus binding to cells is provided in Table 3.

Integrins are targeted specifically to develop therapeutic strategies to treat infections

Integrins are exciting pharmacological targets because (i) they are exposed on the cell surface and are sensitive to pharmacological blockades and (ii) they regulate the interactions of cells and precisely sense their microenvironment. Inhibitors of integrin functions have been successfully tested as drugs to treat several pathological conditions. PSK1404, a nonpeptide antagonist of $\alpha v\beta 3$, inhibited osteoclast-mediated bone resorption in a cancer animal model of bone loss [188]. Volociximab, now known as M200, is a humanized monoclonal antibody that binds specifically to $\alpha 5\beta 1$ integrin [14]. In a phase I trial conducted by Ricart et al., volociximab was shown to stabilize

Table 3 Carbohydrate moieties that interact with viruses

Virus	Viral protein	Carbohydrate moiety	Cell-surface glycoprotein	References
KSHV	Glycoproteins B and K8.1	HS	Proteoglycans	[4, 16]
HSV-1	Glycoproteins B and C	HS	Proteoglycans	[141, 154, 165]
VZV	gB (gpII)	HS	Proteoglycans	[90]
CMV	gB and gM (gC-II)	HS	Proteoglycans	[93, 120]
HHV7	gB and gp65	HS	Proteoglycans	[136, 145]
BPV	Hemagglutinin	Sialic acid and O-linked alpha2,3 neuraminic acids	Sialylglycoproteins and glycophorin A (GPA)	[17, 91]
Human norovirus [23]		Histo-blood group antigens (HBGA) and HS	Glycosphingolipids and proteoglycans	[156, 158]
Vaccinia virus		HS	Proteoglycans	[18]
HIV-1	Subunits gp41 and gp120	Galactosylceramide	Glycosphingolipids and galactosylceramide	[51, 171]
Influenza virus	Haemagglutinin and neuraminidase	Sialyloligosaccharide	Glycoproteins or glycosphingolipids	[144, 187]
JC virus		Sialyloligosaccharide	Glycoproteins or glycosphingolipids	[152]
Sendai virus		Sialyloligosaccharide	Glycoproteins or glycosphingolipids	[59, 109]
Rotavirus virus		Sialyloligosaccharide	Glycoproteins or glycosphingolipids	[34]
Reovirus virus	Sigma1 protein	Sialyloligosaccharide	Glycoproteins or glycosphingolipids	[29]

disease in patients with advanced solid tumors [128]. Vedolizumab, a humanized monoclonal antibody that specifically recognizes the α4β7 heterodimer, underwent a phase 3 trial to determine its effectiveness and safety in treating patients with ulcerative colitis [52]. In that study, vedolizumab as both an initial and maintenance therapy for patients with active ulcerative colitis was shown to be effective in achieving a response and remission [52]. Recently, natalizumab, one of the five therapeutic drugs targeting integrins, has been approved for clinic use. This engineered pan-α4 antibody has been approved for recurrent multiple sclerosis (MS) patients and has been shown to yield promising results for relapsed MS patients by reducing the frequency of relapse, a unique therapeutic result [125]. Its efficacy against Crohn's disease has also been demonstrated [125].

Though integrins have been targeted to treat cancers and other pathological disorders, we have not made a significant breakthrough in targeting integrins to treat virus infections. This does not seem encouraging, especially with many viruses having been shown to utilize integrins to enter cells. This may be due to the fact that (i) viruses utilize multiple receptor molecules to enter the same cell and that (ii) the receptors utilized by the same virus to enter cells *in vitro* and *in vivo* may differ [56]. To overcome this pitfall, we may have to decipher the key elements in the motifs on the virus that interact with integrins and conduct detailed comparative studies outlining the manner by which the virus enters cells under *in vitro* and *in vivo* conditions. This will be crucial for gaining comprehensive knowledge of the receptors utilized by viruses to infect cells. Such studies, we hope, will get us one step closer to developing treatment strategies targeting integrins to combat viral infections.

Conclusions and recommendations

Integrins are just not receptors expressed on the surface of cells. They regulate a diverse set of cellular functions are involved in the pathology of autoimmune diseases [73] and viral infections [174]. Viruses utilize different types of integrins, which are classified primarily based on the manner in which they interact with their ligands, ECM proteins. Integrins physically recognize and interact with distinct amino acid sequences contained within the ligands or pathogens. These can be RGD or any other specific (non-RGD) sequences. Whatever the amino acid recognition sequence may be, integrins (RGD and non-RGD) seem to generally aid in virus attachment and entry into cells. The function of integrins is not limited to providing anchoring for the virus. They are also critical for preparing the cells to support a permissive infection via outside-in signaling. Expression of integrins seems to be of relevance

in the initial infection as well as in the pathobiology of the virus-induced condition. Recent growth in the field of biomedical sciences has already aided in the development of therapeutics based on integrin interactions to treat various cancers and other pathological conditions. To date, such novel therapeutics to treat virus infections are still only a dream, even though multiple viruses seem to utilize integrins to enter cells. Future studies, we hope, will work toward understanding the roles of integrins in virus infection and associated pathogenesis, as such studies may result in novel treatment regimens aimed at preventing the internalization of viruses. After all, the ideal method of treating infection is to block the entry of a pathogen into cells.

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