Virus–Receptor Interactions: Structural Insights For Oncolytic Virus Development

Abstract: Recent advancements in oncolytic virotherapy commend a special attention to developing new strategies for targeting cancer cells with oncolytic viruses (OVs). Modifications of the viral envelope or coat proteins serve as a logical mean of repurposing viruses for cancer treatment. In this review, we discuss how detailed structural knowledge of the interactions between OVs and their natural receptors provide valuable insights into tumor specificity of some viruses and re-targeting of alternate receptors for broad tumor tropism or improved tumor selectivity.

Keywords: oncolytic viruses, virus–receptor interaction, virus entry

Introduction

Oncolytic virotherapy is a dynamic field of cancer treatment with over 70 clinical trials registered to date.1 The majority of oncolytic viruses (OVs) are used in their native, replication-competent form to cause a direct oncolysis of tumors. For instance, coxsackievirus, parvovirus, Newcastle disease virus, measles virus, vaccinia virus and Seneca Valley virus have been used in clinical trials in their native forms.2–6 On the other hand, human pathogenic viruses such as herpes simplex virus-1, poliovirus and adenovirus have been genetically modified to limit their replication to tumor sites and to reduce their virulence in normal tissues.7–9 In addition to the direct oncolysis, OVs can kill cancer cells via several indirect mechanisms: the activation of immunologic pathways and antiangiogenesis.10,11 En route to reaching cancer cells, OV must overcome a range of complex physical and chemical barriers to finally interact with specific cellular receptors.12 Perhaps the most exhaustive obstacle in systemic delivery of OVs is the neutralization of viruses by pre-existing antibodies or triggered anti-viral immune response.13 One way to bypass the host immunity is to mask/manipulate viral surface proteins to avoid recognition by neutralizing antibodies.14,15 However, eliminating antibody recognition does not guarantee a successful infection of tumors with OVs as the cellular uptake will ultimately be dependent on virus binding to the cellular receptors. Expression of virus cellular receptors in cancers varies depending on tumor type as well as among different patients with the same type of cancer.16 In such cases, OV need to be modified to re-target the cancer via alternative receptors. Thus, the manipulation of OV surface proteins to either circumvent anti-viral immune response or to exploit different receptors requires in-depth knowledge of how they interact with their cellular receptors at a structural level. In this review, we discuss the interactions between clinically evaluated OVs and their cellular receptors and how they have been modified to target cancers.
Oncolytic Viruses And Cancer Tropism

Herpes Simplex Virus

Herpes simplex virus 1 and 2 (HSV-1 and HSV-2) belong to the family of Herpesviridae, genus Simplexvirus. HSV virion has a complex architecture characterized by a dsDNA genome, an icosahedral capsid (nucleocapsid), an amorphous layer of protein (tegument) and an envelope (Figure 1A). Both HSV-1 and -2 are genetically stable and considered to be the most serious human pathogens in their family. HSV-1 was shown to be associated with encephalitis and orofacial herpes infections, whereas HSV-2 mostly causes genital infections. The remarkable pathogenicity of HSV is attributed to its ability to establish latent infections in sensory neurons, thus providing a logical reason to manipulate these strains for therapeutic applications.

T-VEC is a genetically modified strain of HSV-1 and represents a major breakthrough in immunotherapy being the first and only US FDA approved oncolytic virus to date. T-VEC is presently used as intralesional injections to treat non-resectable melanoma with many ongoing Phase I/II clinical trials showing the possibility of using the virus in conjunction with other treatments such as immune checkpoint inhibitors. Furthermore, two other strains of HSV-1, G207 (Infected cell protein (ICP) 34.5 and ribonucleotide reductase mutated) and NV1020 (ICP34.5 mutated) have completed Phase I/II clinical trials in malignant brain tumors and in colorectal cancer liver metastasis, showing partial clinical responses and stabilization of metastasis, respectively.

While modifications to the T-VEC genome are aimed at reducing the neurotoxicity of the wild-type strain and stimulating a strong immune response in tumor site, expression levels of cellular receptors and their interactions with HSV still play a vital role in virus entry into tumor cells. HSV utilizes four viral glycoproteins, gB, gD, gH and gL (Figure 1A), expressed on the outer envelope to establish interactions with various cell surface receptors and to facilitate cell entry. In order to initiate HSV cell entry, at least three different classes of cell surface receptors should interact with the respective glycoproteins. Current molecular and structural biology literature identifies three steps in penetrating host cells: 1) gB attachment to heparan sulfate proteoglycans (HSPG), 2) gD binding to nectin-1, herpes virus entry mediator (HVEM), or 3-O-sulfated heparan sulfate, and 3) gB binding to paired Ig-like type 2α (PILRα), nonmuscle myosin IIA (NMHC-IIA) or myelin-associated glycoprotein (MAG) and initiation of envelope fusion with plasma membrane. Upon the envelope fusion with host-cell membrane, HSV nucleocapsid is translocated to the nuclear pore through which viral DNA enters the nucleus.

Figure 1 Structures of enveloped, DNA oncolytic viruses in complex with their cellular receptors. (A) Schematic diagram of herpes simplex virus-1 (HSV-1). (B) HSV-1 utilizes its surface exposed glycoprotein D ectodomain to bind host cellular receptor herpes virus entry mediator A (HveA) ectodomain (PDB: 1JMA). (C) Glycoprotein D of HSV also interacts with the first Ig domain of nectin 1 at 1:1 stoichiometry. Nectin-1 binding site on gD differs from HveA binding site, as evident from the crystal structures arranged in the same orientations (PDB: 3SKU).
Evidence from various clinical studies points toward a direct relationship between the expression of HSV receptors in tumors, cancer progression and prognosis. For instance, herpesvirus entry mediator (HVEM), a member of the tumor necrosis factor (TNF) superfamily, has been shown to play a role in activating inhibitor signaling in T-cells upon binding to BTLA ligand (B-lymphocyte and T-lymphocyte attenuator). Increased expression of HVEM has been reported in hepatocellular carcinoma, gastric cancer and melanoma. Structural evidence for interactions between HVEM and HSV gD protein arises from a crystal structure of gD ectodomain truncated at residues 285 (gD285) bound to the ectodomain of HVEM (Figure 1B). In both HSV-1 and -2, gD is structurally unique in comparison to other members of the family due to diverging N-terminal hairpins. The interface between gD285 and HVEM is comprised of interactions between short, N-terminal hairpin (1–37) that extends towards the V-like immunoglobulin core of gD to establish interactions with two cysteine-repeat-domains (CRDs) of HVEM. C-termini of gD and HVEM are arranged in opposite directions, presumably anchored to viral and cellular membranes, respectively. The observation that only a small segment of gD protein is involved in HVEM binding suggests the possibility of manipulating gD protein to redirect HSV to a different receptor, such as nectin-1 or 3-O-sulfated heparan sulfate, depending on their expression levels in cancers. Nectin-1 is another cell surface receptor that binds gD of HSV. Nectin-1 belongs to the family of nectin or nectin-like receptors that play an important role in cell adhesion. Results from various in vitro and clinical studies have identified increased expression of nectin-1 and nectin-2 in cancers such as breast cancer, highly migratory and invasive carcinoma, squamous cell carcinoma and colorectal cancer. In such instances, nectin-1 serves as an excellent predictor of HSV oncolytic sensitivity. Interactions between gD and nectin-1 have been characterized by crystallization of truncated forms of the gD ectodomain (gD285, truncated residues 1–285) complexed with nectin-1 (Figure 1C). The crystal structure identifies both N- and C-termini and a residue located in Ig core interacting with the first Ig domain of nectin-1 at 1:1 stoichiometry, resembling an interaction pattern similar to nectin-1 homodimers. Interestingly, interactions in gD285-nectin-1 interface are similar to those observed in nectin-1 homodimer interface and distant from gD285-HVEM interface due to the absence of N-terminal hairpin. From a physiological point of view, gD binding to nectin-1 can abolish nectin-1 dimerization, eventually affecting cell–cell adhesion. Therefore, modified HSV strains could have an additional mechanism of hampering tumor progression apart from triggering anti-tumor immunity.

Because of the wide expression of nectin-1 in human cells, targeting nectin-1 expressing tumors with HSV-1 could be problematic in the case of systemic immunotherapy. Such off-target effects can be minimized either by developing HSV mutants capable of escaping nectin-1 while still retaining its ability to bind HVEM, or by identifying potential bi-soluble adapters for targeting cognate tumor receptors. First evidence for latter strategy comes from targeting of epidermal growth factor receptor (EGFR) expressing cells with a HSV variant modified with P-V528LH adapter consisting of gD ectodomain binding region of nectin-1 fused to an EGFR-specific monoclonal antibody.

Vaccinia Virus
Vaccinia virus (VV) is a large, enveloped dsDNA virus (~191 kbp) from the genus Orthopoxvirus of the Poxviridae family. The natural host and origin of VV are not known. Characteristic to VV is its replication strategy which takes place in cytoplasmic viral factories of infected cells. The genome of VV encodes more than 200 proteins, of which approximately 20 are envelope proteins. During the life cycle of VV, three distinct particle types are produced; (1) intracellular mature virions (IMV), (2) wrapped virions (WV) and (3) extracellular enveloped virions (EEV). Mature virions (MV) are stable under virus purification conditions, remaining the most extensively studied form of the virus. By contrast to other dsDNA viruses, IMV has a complex, asymmetric structure that consists of a nucleoprotein core surrounded by a single lipoprotein membrane.

Since its use in eradicating smallpox, VV has played a seminal role as recombinant vectors in gene therapy. Both wild-type and recombinant strains of VV have been of particular interest in oncovirotherapy. As an oncolytic agent, VV has several advantages such as the ability to incorporate a large amount of foreign DNA, fast and efficient replication and safety. Moreover, VV displayed natural cancer tropism, selectively targeting tumors after systemic administration. Clinical trials on VV thus far have employed a potent, yet safe form of VV (JX-594), which encodes granulocyte-macrophage colony-stimulating factor as an immunomodulator.

Vaccinia virus MVs entry into host cells is either mediated by fusion of MV membrane with the plasma membrane at neutral pH or through receptor-mediated endocytosis under
Nonetheless, no receptors have been unequivocally identified. Glycosaminoglycans (GAGs), highly polyanionic compounds present on the surface of stromal tumor cells, have been suggested as putative receptors facilitating VV entry. VV membrane proteins A27L and H3L are essential for fusion of viral membrane with cell membrane. Positively charged amino-terminal of A27L can also act as a site for binding of heparan sulfate (HS). The involvement of additional GAGs such as chondroitin sulfate (CS) in binding the VV surface protein D8L has been shown, but subsequent studies eliminated the essentiality of these receptors. To date, an exact mechanism behind VV-induced oncolysis is unknown. Whether the anti-tumor efficacy is receptor-mediated or attributed to tumor vasculature or whether overexpression of ribonucleotide reductase is essential for viral replication still remains an open question.

Rhabdoviruses

Members of Rhabdoviridae family are enveloped, negative-sense single-stranded (ss) RNA viruses with a 11–15 kb linear genome encoding five proteins: glycoprotein (G), matrix protein (M), phosphoprotein (P), polymerase (L) and nucleoprotein (NP). Rhabdoviruses (RhVs) virions are about 180 nm long and 75 nm wide and have a rod- or bullet-shaped geometry. The G proteindecorating the envelope is involved in receptor binding, whereas NPs are associated with RNA (NP-RNA). Together with L and P, NP-RNA complex forms a ribonucleoprotein particle, which makes contact with M proteins beneath the envelope (Figure 2A).

RhVs have a broad and diverse host specificity with Lyssavirus and Vesiculovirus genera, infecting animals and the remaining RhVs infecting plants. RhVs present several advantages that recommend them for development as oncolytic agents. RhV infections are relatively rare, therefore there is no pre-existing immunity. Additionally, they do not show genetic reassortment, integration in the host genome or malignant transformation due to cytoplasmic replication and have a relative ease of large-scale virus production in a broad range of cell lines. Several RhVs have been investigated for their oncolytic properties.

Vesicular stomatitis virus (VSV) is a vesiculovirus that infects cattle, horses, pigs, and other mammals. VSV infections are usually asymptomatic in human and non-lethal in animals, with mild flu-like symptoms. VSV exhibits a robust infectivity and broad tropism to tumors, attributed to the defective interferon (IFN) responses in tumor cells. Entry of VSV into tumor cells is initiated by the interactions between its coat protein VSV-G (Figure 2A) and highly ubiquitous cellular receptor, low-density lipoprotein receptor (LDLR). LDLR is a transmembrane receptor whose functions include cell-signaling, endocytosis and trafficking of cellular proteins. The most abundantly expressed form of LDLR in solid tumors is LDLR1, shown to be linked to low patient survival rate. The ligand binding domain of LDLR is comprised of cysteine-rich repeats conserved among other members of LDLR family, therefore presenting alternative entry points for VSV. Crystal structures of VSV-G in complex with two different cysteine-rich domains, CRD2 (Figure 2B) and CRD3 (Figure 2C) of LDLR demonstrate that both binding sites on VSV-G are identical. VSV-G-LDLR complex is internalized into host cells through a clathrin-mediated endocytosis. In the case of recombinant VSVΔM51 encoding reovirus fusion-associated transmembrane (FAST) protein, this mechanism extends from the virus-cell fusion to cell-cell fusion. The process repeats, expanding to un-infected cells and could lead to large multineucleated giant cells (syncytia). In another study, the use of VSV-G substituted with lymphocytic choriomeningitis virus glycoprotein (LCMV-GP) has shown minimal neural toxicity and potent anti-tumor effect in mice brain tumor models. LMCV-GP may bind differentially glycosylated α-dystroglycan (αDG) in brain tumors with high-affinity despite the lower expression levels of αDG in human glioblastoma.

Maraba virus is another vesiculovirus which binds LDLR and has the capacity to infect a broad range of human cancers. In order to specifically target cancer cells and to enhance replication efficacy, two mutations were introduced: L123W and Q242R in M and G proteins, respectively. Maraba virus strain MG1 expressing human melanoma-associated antigen-A3 (MAGE-A3) and an adenoviral vector (Ad) expressing the same antigen have been developed as an oncolytic vaccine strategy with high immune priming efficiency.

Newcastle Disease Virus

Newcastle disease virus (NDV) is a ssRNA virus in the genus Avulavirus of Paramyxoviridae family. The enveloped NDV capsid harbours a non-segmented negative-sense ssRNA that codes for six proteins (Figure 2D). Nucleoprotein (NP), phosphoprotein (P) and RNA dependent RNA polymerase (RdRP) bind the RNA genome to form the nucleocapsid. Other NDV proteins include matrix protein (M), which forms the inner layer of virus
envelope, hemagglutinin-neuraminidase (HN) and fusion protein (FP), involved in receptor binding and entry, respectively. Numerous in vitro studies have shown that NDV is non-pathogenic to humans and elicits anti-tumor effects without any genetic modifications or limitations in

Figure 2 Structures of enveloped, RNA oncolytic viruses in complex with their cellular receptors. (A) Schematic diagram of vesicular stomatitis virus. (B and C) Vesicular stomatitis virus (VSV) surface glycoproteins (VSV-G) identify and interact with cysteine-rich domains (CRD) on low-density lipoprotein receptors (LDLR) expressed in cancer cells. Different CRDs interact with VSV-G at identical locations as evident from crystal structures arranged in the same orientation (PDB: 5OLY and 5OY9). (D) Schematic diagram of Newcastle disease virus (NDV). (E) Newcastle disease virus (NDV) surface protein hemagglutinin-neuraminidase (HN) exploits cell surface sialic acid (SA) as the cellular receptors. Two SA binding sites exist on HN dimers, SA1, and SA2 (PDB: 1USR). (F) Schematic diagram of Measles virus (MV). (G and H) measles virus (MV) H binds CD46 short consensus repeats (SCR) 1, SCR2, SCR1-2 interface (PDB: 3INB) and domain 1 of nectin-4 (PDB: 4GJT).
CD46 structure is comprised of a C-terminal domain, a transmembrane domain, a short region with unknown function and four modules of short consensus repeats (SCR) 1-4 at the N terminus. The crystal structure of dimeric H-CD46 identifies interactions between MV-H and SCR1, SCR1-SCR2 interface and SCR2 of CD46 (Figure 2G). CD46 SCR1-2 is pivotal to capsid binding in adenoviruses, discussed later in this review. However, the binding sites of MV-H for CD46 and SLAM overlap, supporting the need to develop strains that can preferentially bind CD46. Two amino acid substitutions, N481Y and S546G in MV-H protein, have been shown to arm MV strains to efficiently use CD46 as an entry receptor in CD46+ cells. In another study, structural characterization of MV-H-nectin-4 complex revealed that the amino-terminal of nectin-4 binds β4-β5 grove of MV-H (Figure 2H). This study identified a hydrophobic pocket located in the groove suggested to be involved in binding all three receptors for MV, with different residues involved for different receptors.

Similar to RhVs, MV exerts its oncolytic activity by a sequence of virus-cell fusion through H protein, cell-cell fusion through F protein and subsequent apoptosis. The Edmonston vaccine strain of MV (MV-Edm) has been modified for non-invasive imaging of MV activity in tumors by introducing either sodium iodide symporter (NIS), the β subunit of human chorionic gonadotropin (hCG) or human carcinoembryonic antigen (CEA) into the MV genome. The MV-CEA strain has been tested in Phase I clinical trials in patients with platinum-resistant ovarian cancer, with evidence pointing towards the recruitment of anti-tumor effector T-cells to establish an anti-tumor immunity. Selective tumor tropism of MV was further validated in a Phase I clinical trial in myeloma, where systemically administered MV-NIS showed replication within tumors. Alternative to live-attenuated vaccines, recombinant, replication-competent MV could be developed to re-target different surface receptors expressed on tumor cells. This requires the mutation of SLAM and CD46 binding sites, thus resulting in a double ablated chimeric H protein to prevent the binding of MV to normal cells expressing SLAM and CD46. Mutations at Y481 and R533 on MV-H and subsequent incorporation of single-chain antibodies directed against cognate receptors such as EGFR has shown to elicit oncolysis of EGFR-positive tumor models in mice.

Measles Virus

Measles virus (MV) is an enveloped, spherical-shaped, negative-sense ssRNA virus (Figure 2F) from the genus Morbillivirus of the Paramyxoviridae family. Due to its highly contagious nature, MV remains a major human health concern worldwide, causing approximately 150,000 deaths annually. Similar to RhVs, the non-segmented RNA genome (15–16 kb in size) of MV encodes five structural proteins: glycoprotein (G), matrix protein (M), phosphoprotein (P), large protein (L) and nucleoprotein (NP). On the MV envelope there are two types of glycoproteins characteristic to paramyxoviruses: 1) hemagglutinin and 2) fusion protein, responsible for cell receptor attachment and fusion, respectively.

Live-attenuated MV vaccine strains can be used as oncolytic agents to target different receptors overexpressed in tumors. Measles virus hemagglutinin (H) binds CD46, signaling lymphocyte activation molecule (SLAM) or nectin-4 in epithelial cells. Overexpression of CD46 and nectin-4 receptors has been identified as a strategy to preferentially target cancers with MV. In addition, SLAM expressed on activated B and T-lymphocytes, monocytes, and dendritic cells has been reported to be the main entry port for wild-type MV.
Adenovirus

Human adenoviruses (HAdVs) belong to the family of Adenoviridae, genus Mastadenovirus and are divided into seven different species from HAdV-A to -G. They are non-enveloped viruses with an icosahedral capsid protecting a dsDNA genome of 26–46 kbp (Figure 3A). The icosahedral capsid is comprised of 252 capsomeres, consisting of 240 hexon trimers and 60 penton bases (PB). Attached to PB plates are trimers of fiber molecules, which utilize the conserved N-terminal (residues 1–20) to bind the PB and the C-terminal knob to bind cellular receptors. Collectively, hexon trimers, PBs, and fiber molecules are known as the major capsid proteins. In addition, 240 copies of the minor protein IX, and several copies of the minor proteins IIIa, VI and VII are located on the capsid exterior and interior, respectively. All the HAdV

Figure 3 Structures of non-enveloped, DNA oncolytic viruses in complex with their cellular receptors. (A) Schematic diagram of human adenovirus (AdV). (B) Coxsackievirus-adenovirus receptor (CAR) extracellular D1 domain interacts with a monomer of AdV12 knob (PDB: 1P69). (C) AdV 11 exploits CD46 as the primary receptor. AdV knob monomer interacts with short consensus repeat (SCR) 1 and SCR1-2 interface. Another knob monomer binds the base of SCR2 (PDB: 3O8E). (D) AdV52 utilizes its short fibers to bind polysialic acid (polySA) and monomer 1 and 3 of the knob trimers interact with two polySA (PDB: 6G47). (E) Desmoglein 2 (DSG2) acts as the receptor for AdV3 with two distinct receptor:knob ratios of 1:1 and 1:2 observed. DSG2 EC2 and EC3 interact with monomer 1 and 2 of AdV3 knob, respectively (PDB: 6QNT). (F) Schematic diagram of human Reovirus (RV). (G) RV exploits cell surface sialic (SA) acid as its attachment receptor to tether the virus in close proximity to host membrane to interact with an entry receptor, junction adhesion molecule-A (JAM-A). SA binds to the stalk of the trimeric sigma protein (PDB: J56X), whereas (H) JAM-A D1 domain interacts with the head of the trimeric sigma protein (PDB: JEOY).
strains can cause gastrointestinal infections, with some subtypes being reported to cause respiratory, urinary tract infections and keratoconjunctivitis. HAdV is also responsible for viral-induced tumors in mice, with subtype A showing the highest oncogenicity, subtype B being weakly oncogenic, while C, E and F are known to be non-oncogenic.

Adenoviruses are one of the most extensively studied viral vectors due to ease of genome manipulation. In addition, HAdVs provide several distinct advantages such as inherently potent lytic activity and feasibility of manufacturing high viral titers. Numerous HAdV strains have been genetically engineered (ONYX-015 and DNX-2401) to reduce infection in normal tissues and to selectively target tumors.

HAdV entry into host cells is a two-step mechanism, which involves the initial attachment of the viral fibers to cell surface receptors, followed by interactions with other capsid proteins and internalization receptors. Upon virus internalization by endocytosis, the capsid escapes into the cytosol through lysis of endosomal membrane and is subsequently trafficked to the nuclear envelope along microtubules, where the viral genome enters the host nucleus via nuclear pores.

Most of the HAdVs and other AdV subtypes except HAdV B use the coxsackievirus and adenovirus receptor (CAR) for cellular attachment. CAR is a type I transmembrane glycoprotein that belongs to the immunoglobulin (Ig) superfamily. It contains a cytoplasmic C-terminal, a hydrophobic transmembrane domain and two extracellular Ig-like domains, D1 and D2. CAR D1 domain alone is sufficient to establish interactions with HAdV fiber knob (Figure 3B). However, the variable expression of CAR in cancers is a significant challenge for HAdV oncovirotherapy. Low expression of CAR was reported for gastric, colon, and prostate cancer cell lines under hypoxic conditions. In addition, CAR expression is downregulated in cancer cells treated with chemotherapy or radiation, which poses an issue when using HAdVs in combination therapies.

The majority of subtype B HAdVs and some of subtype D (AdV37) have been shown to exploit CD46, a type I transmembrane protein overexpressed in tumors, as the attachment receptor. Crystallographic studies showed that AdV11 trimeric fibers form a compact knob that interacts with the SCR1-2 regions of three CD46 molecules (Figure 3C). Complementary or not to CD46, sialic acid has been shown to interact with the top region of AdV37 knob trimer. This has been further confirmed by structural studies on AdV52, which utilizes its long fibers to bind CAR and short fibers to bind polysialic acid (Figure 3D). CD80 and CD86 are another two members from the Ig superfamily that play a key role in subtype B AdV3 entry. Both CD80 and CD86 are expressed in dendritic cells, thus targeting these receptors by AdV can elicit a strong immune response via T-cell activation.

Recent studies have identified desmoglein 2 (DSG2) as a new receptor for HAdV3, HAdV7, HAdV11 and HAdV14 strains of subtype B. DSG2 is a type 1 transmembrane glycoprotein present in epithelial cells that plays an essential role in cell-cell adhesion. The extracellular domain of DSG2 is comprised of four cadherin domains, EC1-EC4, with EC2 and EC3 accounting for the region that binds trimeric fiber knob of HAdV3. DSG2 is overexpressed in a range of epithelial cancers, acting as a marker for targeting such cancers with AdV. A cryo-EM study showed that DSG2 EC2-EC3 fragment binds the top of the trimeric HAdV3 in 2:1 or 1:1 stoichiometry (Figure 3E). EC2 and EC3 establish interactions with the loop regions of monomers 1 and 2, respectively, while the third HAdV monomer of the knob is not engaged. Furthermore, mutagenesis experiments identified D261 as an essential knob residue required for DSG2 binding.

Endocytosis of the HAdV-CAR complex is mediated by the interactions between internalization receptors, integrins and five-fold capsid vertices. Structural information is available on entry receptors avb3 integrins bound to adenovirus, which shows the requirement of Arg-Gly-Asp (RGD) moiety on the penton base to interact simultaneously with several integrins in different orientations to facilitate integrin clustering and subsequent viral entry into host cells via endocytosis. However, mutation of RGD sequence was associated with only a reduced viral infection but not complete abolition. Though no plausible mechanisms have been proposed for an integrin-independent entry pathway of AdV, there is evidence for compensation for loss of penton-integrin interactions through recruitment of fiber receptors. In the absence of sufficient levels of CAR for a successful infection, re-targeting of integrin receptors by incorporation of an RGD moiety in the fiber knob of AdV5 has shown to be efficient in promoting infection of ovarian tumor cells.

Reovirus

Reoviridae is a family of non-enveloped, dsDNA viruses with an icosahedral capsid structure (~85 nm in diameter)
composed of a large outer layer, and a smaller inner layer (Figure 3F). Reovirus (RV) dsDNA is structured into 12 segments, categorized into three size-dependent groups: large, medium and small. The outer shell of the capsid and at the vertices of the virion are formed by heterodimers of µ1 and σ3 proteins, while pentamers of λ2 protein form a channel connecting to trimers of attachment protein σ1.

RV requires interactions with junctional adhesion molecule-A (JAM-A) and cell surface monosaccharides such as sialic acid to penetrate the host cell. JAM-A expression has been proposed to be linked to tumor cell proliferation and progression, whereas in some cases an inverse relationship was observed. The first step of the RV binding to host cells involves a low-affinity interaction of the lower part (stalk) of σ1 protein with cell surface sialic acid (Figure 3G). This process facilitates the anchoring of RV capsid in close proximity to host-cell membrane in order to initiate interactions with a secondary receptor. High-affinity interactions between JAM-A D1 domain and the head domain of σ1 protein (σ1H) serve as the second step in RV host-cell attachment (Figure 3H).

Reolysin, a wild-type, non-pathogenic, serotype 3 RV, has been widely investigated in preclinical and clinical settings. Phase I and II clinical trials of advanced solid tumors and recurrent gliomas, and combination therapy with paclitaxel/carboplatin or docetaxel showed Reolysin to be safe and effective.

**Parvovirus**

Human parvovirus (HPV) is a single-stranded DNA virus in the Parvoviridae family, associated with a wide variety of diseases in humans. The genome of HPV is packaged inside an icosahedral capsid of ~280 Å in diameter. The capsid is composed of 60 structural subunits, in which major capsid protein VP2 is the primary protein (~95%) while the minor capsid protein VP1 is less abundant (~5%). Capsid proteins have an eight-stranded, antiparallel β-barrel “jelly roll” fold. Engineered and wild-type strains of HPV demonstrate a tumor-selective replication with excellent safety profiles. Oncolytic activity of HPV is attributed to the direct oncolysis as well as induced antitumor immunity.

HPV B19 strain binds the erythrocyte P19 antigen expressed in erythroid progenitor cells. However, entry into host cells requires the involvement of α5β1 integrin co-receptor, known to be essential for tumor progression in certain cancers. Modifications of I367S and H373R in the dimple region of the capsid in rat parvovirus strain H-1PV have engineered the virus to re-target integrin receptors expressed in cancers. In another study, transferrin receptor 1 (TFR1) has been identified as the cellular receptor for canine parvovirus (CPV). TFR1 is a membrane glycoprotein linked to many diseases including cancers. However, TFR1 expression is variable across different cancers. The structure of CPV-TFR1 complex demonstrates an example for a receptor saturating only a few of the 60 equivalent binding sites on the capsid, resulting in an asymmetric interaction.

**Coxsackievirus**

Coxsackievirus (CV) is a non-enveloped, positive-sense ssRNA virus (~7.4 kb) from the family of Picornaviridae, genus Enterovirus (Figure 4A). CV is a major human pathogen causing a number of diseases including myocarditis and meningoencephalitis. CV serotypes are categorized into two groups; (1) coxsackievirus A (CVA) and coxsackievirus B (CVB). CV RNA genomes code for four structural proteins VP1–VP4 that form an icosahedral capsid, and seven non-structural proteins. Characteristic to enteroviruses is the presence of four types of particles in their life cycle: mature virion, procapsid devoid of RNA, an expanded A-particle and an empty particle after RNA exit.

Receptor binding in enteroviruses takes place in the “canyon”, a depression located at 5-fold axis of the capsid. The binding of the receptor displaces a fatty acid molecule called the “pocket factor” located in a hydrophobic pocket within VP1, below the canyon base. Loss of the pocket factor induces a series of conformational changes in capsid architecture, leading to capsid expansion and externalization of VP1 N-terminus as well as VP4 for membrane anchoring and subsequent RNA transfer. This mechanism holds true for most of the enteroviruses and has been well characterized for poliovirus (PV), enterovirus 71 (EV71) and CV.

CVs utilize three different receptors for cellular entry. CAR acts as both attachment and entry receptor for CVB3. Cryo-EM reconstruction of CVB3 bound to full length human CAR has shown that the N-terminal region of CAR D1 domain contains the binding sites for CVB3 (Figure 4B). In the CVB3-CAR interface, A and G β strands of D1 domain form contacts with the north and south rims of CVB3 canyon. All the external CVB3 capsid proteins are involved in CAR binding with majority of the interactions localized to VP1. Of note is the moderately conserved nature of these receptor binding residues across
six different CVB serotypes. VP2 residue N165 has been suggested to be critical in stabilizing the electrostatic interactions between the capsid and CAR. The distal end of CAR D1 domain is a shared site for CVB3 and adenovirus (as previously discussed) and their binding sites overlap on C β strand and FG loop. Additionally, the involvement of decay-accelerating factor (DAF) as an attachment receptor in the CVB3-RD strain has been demonstrated by another cryo-EM study, with one DAF molecule linking two adjacent protomers on the capsid exterior. The northern end of the VP2 puff (residues 129–180) in one protomer is linked to the south end of the
Poliovirus entry into host cells is initiated by the interactions between poliovirus receptor CD155, and capsid canyon.\(^{217-220}\) PV undergoes the same conformational changes characteristic to other enteroviruses. A-particle formation,\(^ {194,221}\) exit of RNA genome at a location on 2-fold axis\(^ {193}\) and empty particle formation\(^ {222}\) have been extensively characterized. CD155 is an onco-immunologic protein overexpressed in human cancers with a role in tumor cell invasion and migration.\(^ {223}\) CD155 is a type I immunoglobulin-like transmembrane protein that contains three ectodomains D1–D3.\(^ {218,224}\) CD155 expression is upregulated in carcinomas\(^ {225-227}\) and less abundantly expressed in normal tissues with the exception of liver development or regeneration.\(^ {228}\) In the PV-CD155 complex (Figure 4E), the D1 domain of CD155 binds VP1, and VP2 of one protomer and VP3 of adjacent protomer at the capsid quasi 3-fold axis.\(^ {219}\) In the PV capsid, C-terminal, GH, EF, BC loops, C β strand of VP1, B β strand, GH loop of VP3 and EF loop of VP2 occupy the CD155 binding site.

Poliovirus infection is rapid and remarkably efficient, releasing as high as 10,000 mature virions per infected cell at 6 hrs post-infection.\(^ {229}\) Even though a rapid replication warrants the applicability of PV in oncovirotherapy, a counter mechanism must be in place to minimize the neurotoxicity associated with wild-type PV. The neuro-attenuated variant of PV, PVSRIPO has completed a Phase I dose-finding clinical study in patients with grade IV malignant glioma with no neurotoxicity reported.\(^ {230}\)

**Seneca Valley Virus**

Seneca Valley Virus is the only member of *Senecavirus* genus of the *Picornaviridae* family. The overall structure of SVV has an icosahedral symmetry and is comprised of a non-enveloped protein capsid harboring a positive-sense ssRNA genome of approximately 7.3 kb (Figure 4F).\(^ {231}\) Similar to CV and PV, the SVV genome encodes seven non-structural proteins and four structural proteins. To date, the SVV strains have been classified into 3 clades,\(^ {232-234}\) with the prototype SVV-001 being the sole member of clade I.

SVV cell entry is dependent on its cellular receptor: anthrax toxin receptor 1 (ANTXR1), also known as tumor endothelial marker 8 (TEM8).\(^ {235}\) ANTXR1 is a type I transmembrane protein overexpressed in many types of cancers, but weakly expressed in healthy tissues.\(^ {236}\) The role of ANTXR1 is unknown beyond its function as a toxin and virus receptor; indeed, ANTXR1 knockout mice exhibit no major phenotypic abnormalities.\(^ {237}\)
However, ANTXR1 blockade has been shown to decrease tumor angiogenesis and to potentiate an anti-tumor effect towards certain cancers.236 Our group identified the surface exposed loops on SVV-001 capsid exterior, BC loop, loop II of VP1, the “puff” loop of VP2, and the “knob” loop of VP3 which form the binding site for the extracellular domain of ANTXR1 (Figure 4G).237 Furthermore, we showed that SVV binding site on ANTXR1 is non-conserved in its paralogous receptor, ANTXR2, which is expressed in normal cells, thereby providing a structural basis for tumor specificity of SVV.240 SVV empty capsid binds ANTXR1, suggesting it may have potential as a vaccine or as virus-like particles for the development of tumor-targeted delivery of drugs.240

As suggested from both functional and structural studies, the tumor tropism of SVV-001 is attributed to receptor-mediated internalization of the virus, a phenomenon common to other oncolytic picornaviruses. However, a successful SVV-001 infection may also require an additional innate immune defect.235 SVV-001 in its native form provides several advantages for oncovirotherapy: the native virus is genetically stable and non-toxic to healthy tissues, it is safe and it homes to tumors when administered systemically and pre-existing immunity for SVV is rare.241 Several preclinical, Phase I/II clinical studies have demonstrated the anti-tumor potential, intratumoral replication and safety of SVV in treating solid tumors with neuroendocrine features.242,243

Conclusion
Oncolytic viruses (OVs) either have an inherent ability to successfully replicate in cancer cells or they have been modified to exploit de-regulated signaling pathways in tumors. Nevertheless, the attachment of OVs to specific receptors found in cancers plays a pivotal role in OV tumor cell entry, subsequent viral replication and cell lysis. However, the expression of these receptors varies in different cancers and also among individual patients. Furthermore, the presence of natural receptors of OVs in normal cells may pose a potential challenge when the virus is pathogenic in nature. Therefore, understanding the structural details concerning how OVs interact with their receptors can inform the development of more efficient-targeted therapies to exploit cognate receptors and to reduce off-target cytotoxicity. Additionally, oncovirotherapy is constantly facing the challenge of overcoming antiviral immunity in cancer patients. In this case, the knowledge of OV-receptor interactions is necessary to modify the viral capsid or envelope proteins in order to bypass the immune response without impairing the ability to bind their cellular receptors.

Disclosure
Dr John T Poirier reports personal fees from Perceiver Pharmaceuticals LLC, outside the submitted work. In addition, Dr Poirier has a patent WO2017096201A1 licensed to Perceiver Pharmaceuticals, LLC. The authors report no other conflicts of interest in this work.

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