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Several structures of complexes between viral attachment proteins and their cellular receptors have been determined recently, enhancing our understanding of the molecular recognition processes that guide formation of virus–receptor complexes. Moreover, these structures also highlight strategies by which highly similar viral proteins within a single virus family can adapt to engage different receptors. Consequences of such differences are altered tropism and pathogenicity. An improved understanding of the molecular details of this specificity switching in receptor binding will help to establish links between receptor tropism, spread, and disease. Moreover, it also has relevance for the design and use of viruses as gene delivery vehicles with altered properties as well as for the identification of target viral epitopes of new vaccines.

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**Introduction**

The interaction between a virus and a host cell receptor is the first step in a complex process that eventually leads to cell infection. Viruses must not only be able to specifically attach to cells in order to gain entry into the cell, but their newly formed progeny must also be able to release themselves from the cell membrane after an infection. As a result, attachment and release processes depend on accurately regulated contacts and affinities between viral proteins and their cognate receptor molecules on the cell surface. However, these interactions are constantly subject to changes because of evolutionary pressure on viruses to increase their infection efficiency [1]. Subtle modifications in the virus coat proteins can have drastic consequences, leading to the emergence of a new pathogen with altered infectivity, tissue tropism, or host range. Well-established examples of such modifications include strains of several picornaviruses such as foot-and-mouth disease virus, human rhinoviruses, and coxsackieviruses, all of which can be adapted to use an alternate receptor for cell entry in tissue culture [2–4]. Another example is the canine parvovirus, which has emerged as a new pathogen of dogs by gaining the ability to recognize the canine transferrin receptor [5]. Finally, measles virus and the SARS coronavirus are also established models for receptor specificity switching as a result of subtle amino acid changes in their viral attachment proteins [6,7]. A number of well-resolved structures of viruses or viral proteins in complex with cellular receptors are available, and several of these have already contributed to our understanding of parameters that can alter ligand specificities [7–22,23,24,25,26,27,28,29,30,31,32,33,34]. In this review, we will focus on three examples: adenoviruses (Ads), paramyxoviruses, and polyomaviruses. In each case, recent structural information has allowed for an improved appreciation of strategies used by these viruses to engage different receptors.

**Interactions of adenoviruses with their cellular receptors CAR and CD46**

Ads are nonenveloped, icosahedral particles that have a trimeric attachment protein, or fiber, protruding from each of the 12 vertices of the capsid [35]. The fiber consists of a globular head (the knob), a fibrous shaft, and a tail. Fifty-one Ad serotypes, belonging to subgroups A–F, are currently known, and they cause a wide range of diseases in humans [35]. While many Ads attach to cells by engaging the coxsackievirus and adenovirus receptor (CAR) [16,36] or sialic acid [14,37], most group B serotypes use the ubiquitously expressed membrane cofactor protein (MCP) CD46 as their receptor [38–40]. The extracellular region of CD46 contains four ~60 amino acid units known as short consensus repeats (SCR1–SCR4). The crystal structure of the SCR1–SCR2 region of CD46 in complex with the Ad11 knob revealed that the Ad11 knob profoundly realigns the overall conformation of CD46, reshaping its bent surface structure into an elongated rod [25,26]. This conformational change is in part mediated by the extrusion of a single hydrophobic residue from the interface between two CD46 domains. A centrally positioned arginine side chain serves as the primary determinant of binding [41].

The location of the CD46-binding surface is completely distinct from that used by other Ads to bind to CAR (Figure 1a and b). The structure of the complex
Ad12 knob and CAR [16] showed that the Ad12 knob AB-loop serves as the most important determinant of CAR binding as it contributes over 50% to the protein–protein interaction, including three hydrogen bonds involving residues that are conserved in CAR binding Ads serotypes. The elongated AB-loop forms a platform that spans the width of CAR. By comparison, CD46 engages a long and narrow surface formed by the DG-loop, HI-loop, and JJ-loop from two protomers in the Ad11 knob [25**]. The CAR-binding AB-loop is located on a different face of the knob, almost exactly opposite from the site of CD46 attachment. While the overall structures of the Ad11 and Ad12 knobs are very similar, closer inspection of the binding regions for CD46 and CAR reveals that each knob has subtly altered its loop structure in order to gain specificity for its receptor. Non-CAR-binding Ad knobs typically carry an insertion in the AB-loop, which, in the case of Ad11, protrudes from the core β-sheet and likely helps to prevent binding to CAR. Superposition of the Ad12 knob–CAR complex with the Ad11 knob brings the
most protruding Ca-atom of the Ad11 AB-loop into very close proximity to the nearest Ca atom of CAR (Figure 1c and e). The distance between the Ca atoms is only about 4 Å, which effectively would prevent CAR from forming a complex with the Ad11 knob in a manner similar to the interaction seen in the Ad12 knob–CAR complex. Conversely, CAR-binding Ad knobs have very short DG- and HI-loops, lacking most of the CD46-binding surface (Figure 1d and f). Interestingly, the modes of CAR and CD46 binding are quite different. The CAR-binding surface of Ad12 features several discrete, smaller contact points separated by large solvent-filled cavities [16], whereas the CD46-binding surface in the Ad11 knob is extensive, continuous, and devoid of solvent molecules [25**]. Despite these differences, both adenovirus types feature large buried surface areas and bind to their respective receptors CAR and CD46 with high affinity [25**,42]. Ads therefore have evolved to bind different receptors not by adjusting an initial binding surface but by creating an alternative second one while deconstructing the first.

### Cellular receptor recognition in the paramyxovirus family

The paramyxoviruses are enveloped, negative-stranded RNA viruses that include relevant human and animal pathogens [43]. In the viruses of the paramyxovirus family, cell attachment and virus–cell membrane fusion are mediated by two distinct membrane glycoproteins. The proteins responsible for cell attachment, which will be the focus of this section, exhibit some diversity at the functional level as well as at the level of the cellular receptor to which they bind. Rubulaviruses (e.g. Mumps virus), avulaviruses (e.g. Newcastle disease virus), and respiroviruses (e.g. Sendai virus) bind to cell surface sialic acid via the hemagglutinin–neuraminidase (HN) attachment glycoprotein, a bifunctional protein engaged in recognition as well as hydrolysis of sialic acid. Both activities are absent in other paramyxoviruses such as the morbilliviruses (e.g. measles virus), henipaviruses (Hendra and Nipah viruses), and pneumoviruses (e.g. respiratory syncytial virus) [43]. These latter viruses recognize protein receptors via the hemagglutinin (H) glycoprotein in morbilliviruses or the attachment glycoprotein G in henipaviruses and pneumoviruses.

The paramyxovirus attachment proteins are type II membrane proteins anchored to the virus envelope by a single transmembrane domain [43]. Their extracellular region can be divided into an N-terminal stalk region that serves as a spacer, and a C-terminal globular domain that has receptor-binding activity. In the virus envelope, the attachment proteins are present as disulphide-linked homodimers, and there are indications of tetramer formation in some cases [44–46]. The attachment proteins form complexes with the fusion (F) proteins, which are also located in the viral envelope. Receptor binding must trigger rearrangements in these complexes that alter the structure of F and result in fusion of the viral and cellular membranes at neutral pH [47].

The C-terminal, globular domains of paramyxovirus HN glycoproteins from Newcastle disease virus (NDV), human parainfluenza type III (PIV3), and parainfluenza virus 5 (SV5) all fold into highly similar six-bladed β-propeller structures [12,13,21]. The high degree of similarity is confirmed by the structural alignment shown in Figure 2. Recent work by several groups has now resulted in crystal structures of three additional paramyxovirus attachment glycoproteins: measles virus H (MV-H) [26**,27**) as well as Nipah virus G and Hendra virus G (NiV-G and HeV-G, respectively) [29**,30**]. As NiV-G and HeV-G are very similar, only NiV-G will be discussed in detail here. The MV-H and NiV-G structures superimpose well with those of the previously determined HN proteins (Figure 2), although, as noted before [29**], the agreement with NiV-G is somewhat better compared to MV-H. Despite these structural similarities, NiV-G and MV-H function very differently from the HN proteins as they lack the conserved residues engaged in sialic acid binding and hydrolysis (red in Figure 2). Instead, NiV-G interacts with the ephrin-B2 (EFNB2) and ephrin-B3 (EFNB3) receptors [48,49], whereas MV-H can bind either CD46 [50,51] or Signaling Lymphocytic Activation Molecule (SLAM) [52], depending on the MV strain. Thus, a specificity switch from carbohydrate to protein receptor is seen in NiV-G as well as in MV-H. Interestingly, however, the strategy that made this switch possible is very different in the two cases.

Structures of complexes between NiV-G in complex with both EFN B2 and EFN B3 receptors are available [29**,30**], allowing for a detailed comparison of the NiV-G receptor binding mode with that of the sialic acid binding HN proteins (Figure 3). The receptor-binding surfaces in HN and NiV-G overlap, and both sialic acid and the EFN B2/EFNB3 receptors bind to sites at the recessed center of the respective β-propeller [29**,30**]. Protruding hydrophobic residues at the long GH-loop of EFN B2 interact with residues in NiV-G that lie very close to the sialic acid binding site in HN (Figure 3). Thus, NiV-G has an altered contact surface at the center of the propeller. Interestingly, engagement of EFN B2 is accompanied by conformational changes in two NiV-G surface loops that carry EFN B2-contacting residues [53*]. These loops appear to be rather flexible in the unliganded NiV-G structure and only lock into place upon engagement of EFN B2. As only the structure of unliganded MV-H is known so far, we have to rely on receptor-binding data to discuss the putative location of the CD46-binding and SLAM-binding sites on this protein. Both receptor-binding sites map onto the side of the MV-H propeller [26**,27**) (blue in Figure 3). The putative receptor-binding region in MV-H includes the end of the fourth blade and the
beginning of the fifth blade in the β-propeller, a region that exhibits the largest structural difference between MV-H and the other paramyxovirus proteins (Figure 2). This region lacks glycosylation specifically in MV-H (underlined in Figure 2), and thus represents an appealing place for interactions. Indeed, both MV receptors bind to overlapping sites [54] that are now mapped in this region. In contrast, MV-H carries a glycan linked to Asn215 facing

Structural alignment of the parvovirus cell attachment proteins. The β-propeller domains of the indicated protein structures were aligned with the program Modeller (program website: http://salilab.org/modeller/modeller.html) with a gap penalty of 1.75. β-Strands and α-helices are represented with arrows and rectangles, respectively. The four β-strands forming each blade are labeled s1–s4, and the six blades in the propeller are labeled β1–β6. Residues engaged in sialic acid binding by the HN proteins are boxed in red [12,13,21], residues involved in binding to the EFNB2/EFNB3 receptors by the NiV-G protein are in orange [29,30], and some of the MV-H residues engaged in binding to the CD46 and SLAM receptors are shown in light and dark blue, respectively, whereas residues interacting with both receptor proteins are medium blue [26,27]. Glycosylation sites are underlined.
toward the center of the β-propeller [27**]. Thus, the region used by both the HN and NiV-G proteins for interactions with their receptors is effectively closed off for binding in MV-H. Compared with the NiV-G protein, MV-H therefore uses a different strategy to engage its cellular receptors. It does not modulate the binding surface at the top of the β-propeller, but instead creates a new one at its side. Glycans are being used as determinants of receptor binding in MV-H by shielding one possible binding region and exposing another.

**Ganglioside receptor recognition by the polyomaviruses**

Polyomaviruses are a group of small, nonenveloped DNA viruses that can infect birds, rodents, and primates. Members of the group include simian virus 40 (SV40) and murine polyomavirus (Polyoma) as well as a number of human polyomaviruses such as the BK and JC viruses (BKV and JCV, respectively). Recently, a new human polyomavirus was found to be linked to Merkel cell carcinoma, an aggressive type of skin cancer [55†]. All polyomavirus capsids are constructed from 360 copies of the major coat protein, VP1, arranged in pentamers on a $T=7$ icosahedral lattice [56]. The cell surface receptors for SV40, Polyoma, and BKV are gangliosides, complex, sialic acid containing sphingolipids that reside primarily in lipid rafts. SV40 uses the ganglioside GM1, whereas BKV binds GD1b and GT1b, and Polyoma attaches to GD1a and GT1b [57,58]. Structures of complete Polyoma particles and of Polyoma VP1 pentamers in complex with ganglioside receptor fragments [9,59] revealed that VP1 binds the oligosaccharide portions of the gangliosides in shallow surface pockets that are formed by extensive loops at the outer edge of the capsid. The recently determined structure of the structurally conserved SV40 VP1 pentamer in complex with GM1 [28**] shows that SV40 recognizes its ligand at a similar location on the outer surface of VP1. The Polyoma and SV40 receptors both feature a terminal sialic acid connected to a galactose via an α2,3 glycosidic linkage, and this structural motif is bound by essentially the same region of the capsid.

Although the VP1 surface loops exhibit relatively high sequence variability among polyomaviruses, key residues between SV40 and Polyoma are conserved. For example, a central contact between the sialic acid and Polyoma VP1 is mediated by Arg77, which is replaced with Lys67 in SV40. One would therefore expect to also see at least partially similar contacts in both cases. Strikingly, however, the sialic acid–galactose moieties are bound in completely different orientations to the two proteins (Figure 4). In Polyoma, the sialic acid carboxylate faces away from the fivefold axis of the pentamer, forming a key salt bridge with Arg77, and the glycerol side chain points away from the virion into solution. In SV40, the sialic acid glycerol chain in GM1 faces toward VP1, whereas its carboxylate group faces toward the fivefold axis and does not engage in a salt bridge that would neutralize its charge. The Lys67 side chain in SV40 does not contact the sialic acid but instead forms the ridge that separates the binding pockets for the two branches of GM1. The residues that stabilize the conformation of Arg77 in Polyoma, Gln59 and Tyr72, correspond to Asn57 and Gln62 in SV40, respectively, which are unable to make similar interactions with Lys67. As a result, Lys67 is held in place by Asp81, which is equivalent to Gly91 in Polyoma. Residues at equivalent positions in the sequence and in space therefore perform drastically different tasks in SV40 and Polyoma. Thus, two highly homologous viruses that probably have a similar origin evolved to use distinct receptor-binding motifs for the recognition of highly similar receptor molecules.
Conclusions
Within a family of viruses, one frequently finds a number of virus subtypes that vary in cellular tropism and pathogenicity. In many cases, these altered properties can be directly linked to small changes in the coat protein structure that switch specificity from one receptor to another. Structural data on one virus–receptor complex rarely allow for a prediction of how a closely related virus would engage a different receptor. However, the comparison of similar viruses in complex with different receptors has become possible through the structure determination of several virus–receptor complexes. As we have shown here, such a comparison does provide some clues about the strategies by which viruses switch their specificity. We find that, in several cases, exceedingly small changes in surface structure are used to modulate receptor-binding interactions. Binding sites can be deconstructed by simply inserting one residue into a loop, as seen in the Ads that no longer bind CAR, or by subtle modifications that change the binding specificity from sialic acid to a protein receptor, as seen in the paramyxovirus glycoproteins HN and G. Similarly, binding to receptors can be modulated, in part, through the introduction of glycans at strategic positions, as seen in the MV-H glycoprotein. Finally, there exists surprising variability in the mode of viral coat protein binding to sialylated oligosaccharides. These compounds can be recognized by structurally very similar proteins, such as the variants of the polyomavirus VP1 molecules, through highly distinct binding motifs. The available structural database is becoming large enough to perhaps also advance an understanding of specificity switching in related cases where detailed structural information is still lacking.

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