Polysialic acid is a cellular receptor for human adenovirus 52

Human adenovirus 52 (HAdV-52) is one of only three known HAdVs equipped with both a long and a short fiber protein. While the long fiber binds to the coxsackie and adenovirus receptor, the fiber domain of the short fiber in the virus life cycle is poorly understood. Here, we show, by glycan microarray analysis and cellular studies, that the short fiber knob (SKF) of HAdV-52 recognizes long chains of α-2,8-linked polysialic acid (polySia), a large posttranslational modification of selected carrier proteins, and that HAdV-52 can use polySia as a receptor on target cells. X-ray crystallography, NMR, molecular dynamics simulation, and structure-guided mutagenesis of the SKF reveal that the nonreducing, terminal sialic acid of polySia engages the protein with direct contacts, and that specificity for polySia is achieved through subtle, transient electrostatic interactions with additional sialic acid residues. In this study, we present a previously unrecognized role for polySia as a cellular receptor for a human viral pathogen. Our detailed analysis of the determinants of specificity for this interaction has general implications for protein–carbohydrate interactions, particularly concerning highly charged glycan structures, and provides interesting dimensions on the biology and evolution of members of Human mastadenovirus G.

Human adenoviruses (HAdVs) are common human pathogens associated with gastrointestinal, ocular, and respiratory infections. To date, 84 different HAdV types have been identified, and they are grouped into seven species (Human mastadenovirus A to G) (1). HAdVs are nonenveloped viruses whose icosahedral capsid is composed of three major proteins, the fiber, the penton base, and the hexon, all of which are known to mediate binding to host cells. The fiber protein, with a terminal knob domain, binds to cellular receptors such as the coxsackie and adenovirus receptor (CAR) (2–4), desmoglein-2 (5), CD46 (6–8), or sialic acid (Sia)-containing glycans (9–11). The penton base interacts with cellular integrins, thereby facilitating endocytosis (12, 13) and endosomal release (14, 15). The hexon protein is the main component of the viral capsid and binds with high affinity to coagulation factors IX and X, resulting in liver tropism through indirect binding to heparan sulfate on hepatocytes (16–18), and shields the virion from neutralizing antibodies and complement-mediated destruction (19).

HAdV-52 was isolated in 2003 from a small outbreak of gastroenteritis (20). The virus diverged from other HAdVs and was classified into the new species Human mastadenovirus G (HAdV-G), which otherwise exclusively contains Old World monkey AdVs. HAdVs are normally equipped with only one fiber protein, but HAdV-52, along with species HAdV-F types HAdV-40 and -41, differ from all other known HAdVs by having two different fiber proteins, one short (coded by gene fiber-1) and one long (fiber-2) (20–22). We showed recently that the knob domain of HAdV-52 long fiber (52LFK) binds to CAR and that the knob domain of the short fiber (52SKF) binds to Sia-containing glycoproteins on target cells (23). However, the identity and structure of the cellular Sia-containing glycans have remained unknown.

Sia-containing glycans serve as receptors for a large number of viral pathogens, including influenza A virus, coronavirus, rotavirus, polyomavirus, and many others (24). Variations in Sia specificity determine host and tissue tropism, pathogenicity, and transmission of multiple viruses. Here, we show by glycan microarray analysis that the 52SKF recognizes long chains of sialic acid residues, known as polysialic acid (polySia), with higher affinity than any other tested glycan. Polysialylation is a rare posttranslational modification of only nine identified carrier proteins to our knowledge; among them are the cell adhesion molecules NCAM (25) and SynCAM-1 (26) as well as Neurogliin-2 (27) and the dendritic cell chemokine receptor CCR7 (28). Polysialylation is best known as a modulator of developmental plasticity in the nervous system, but more recently, additional roles in gene therapy of these cancers.

Significance

We present here that adenovirus type 52 (HAdV-52) attaches to target cells through a mechanism not previously observed in other human pathogenic viruses. The interaction involves unusual, transient, electrostatic interactions between the short fiber capsid protein and polysialic acid (polySia)-containing receptors on target cells. Knowledge about the binding interactions between polySia and its natural ligands is relatively limited, and our results therefore provide additional insight not only into adenovirus biology but also into the structural basis of polySia function. Since polySia can be found in high expression levels in brain and lung cancers where its presence is associated with poor prognosis, we suggest that this polySia-binding adenovirus could be useful for design of vectors for gene therapy of these cancers.

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Data deposition: The crystallographic dataset of the relevant protein/glycan complex structure has been deposited in the RCSB Protein Data Bank (PDB), www.rcsb.org/pdb/ (6G47).

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the development of a number of organs, such as the liver, kidney, heart, and testes, have been unraveled (reviewed in ref. 29). In the adult brain, polySia expression is markedly down-regulated and only retained in few areas that maintain plasticity such as the hippocampus, olfactory bulb, and hypothalamus (reviewed in refs. 30–32). However, polySia is not exclusively associated with the brain. Recent studies demonstrate additional regulatory roles in innate immune responses (28, 33–36), and in regenerative or antiinflammatory processes (37–42). Furthermore, polySia is found at high expression levels on several types of cancer including glioma (43–45), neuroblastoma (46, 47), and lung cancer (48, 49). By means of X-ray crystallography, NMR, molecular dynamics (MD) simulation, and cellular analyses, we reveal here a function for polySia as a cellular receptor for HAdV-52. The 52SFK possesses a unique polySia-binding mode featuring transient polar interactions and electrostatic contributions that extend beyond a fixed anchoring epitope engaging the non-reducing end of the polySia chain. We further provide an evolutionary analysis of the newly found polySia binding pocket within Human mastadenovirus G.

Results
HAdV-52 Short Fiber Knob Binds to PolySia. We showed previously that the binding of HAdV-52 to human epithelial cells is sialic acid dependent and occurs via the SFK (23). To date, the precise compositions and structures of glycans that can be optimally engaged by 52SFK remain unknown. We performed glycan microarray analysis of 52SFK with 128 different sialylated glycans, in an attempt to characterize the glycan receptor of HAdV-52. Very strong binding signals were observed with 52SFK for a group of linear α-2,8-linked oligoSia that represent fragments of naturally occurring polySia (Fig. 1 and Table S1). The maximal response was observed at a degree of polymerization (DP) greater than 3 (DP5 to -9). This binding was much greater than for α-2,3- and α-2,6-linked sialic acids in the array. The relatively weak binding detected with the probe oligoSia DP3 is likely to be due to the ring-opened status of the core monosaccharide as a consequence of the reductive amination procedure used for preparing the neoglycolipid probe (50). This suggests that the high-affinity interaction with 52SFK requires at least three intact α-2,8-linked sialic acid residues. To confirm the ability of 52SFK to interact with polySia and to evaluate the specificity of this interaction, we developed an ELISA with immobilized, Escherichia coli-derived polySia (colominic acid; DP ∼ 80–100) and analyzed the binding of recombinant knob domains from HAdV-52 short fiber, the Sia-binding HAdV-37 fiber (37FK), and the CAR-binding HAdV-5 (5FK) and HAdV-52 long fiber (52LFK). The 52SFK bound efficiently to polySia, while the two CAR-binding FKs did not show any binding to this compound (Fig. 2A). 37FK, which binds with relatively high affinity to the branched, disialylated GD1a glycan using a different binding site (11, 23), bound less strongly to polySia than 52SFK. We therefore conclude that HAdV-52 is able to interact preferentially with polySia.
with polySia via the knob domain of its short fiber while having low affinities for a number of monosialylated glycans.

**HAdV-52 Binds to PolySia on Human PolySia-Expressing Cells.** To test the relevance of polySia recognition by HAdV-52 in a cellular context, we used the human polySia-expressing indoloma cell line SH-SY5Y and its polySia-lacking parental cell line SK-N-SH as models for virus binding and infection (51). The levels of polySia on these cells were confirmed by flow cytometry using the anti-polySia antibody mAb735 (Fig. S1). 52SFK gave five times higher binding signals with polySia-expressing SH-SY5Y cells compared with the control cell line, whereas none of the control knobs, including 37FK, showed a comparable interaction pattern (Fig. 2B). Next, we used monosialic acid-binding lectins to evaluate the relative levels of glycans with terminal sialic acids on the two cell lines to exclude the possibility that the higher 52SFK binding to SH-SY5Y was due to a higher level of glycans with terminal monosialic acids on these cells rather than preferential binding to polySia. All three lectins tested, *Maackia amurensis* I and II (MAL I and II; binds to α-2,3-linked Sia), *Sambucus nigra* lectin (SNA; binds to α-2,6-linked Sia), and wheat germ agglutinin (WGA; binds to terminal sialic acid as well as to N-acetyl-D-glucosamine) bound stronger to SK-N-SH cells than to SH-SY5Y cells (Fig. S1), indicating that the parental, polySia-negative SK-N-SH cells have a higher total density of terminal sialic acids. Furthermore, preincubation of 52SFK with soluble oligoSia (DP5) reduced 52SFK binding to SH-SY5Y cells up to 75%, while no effect was observed on 37FK binding (Fig. 2C). Preincubating the whole HAdV-52 virions with oligoSia (DP5) also efficiently reduced binding to and infection of SH-SY5Y cells, whereas sialic acid monosaccharide (DP1) did not have as much of an effect (Fig. 3A and C). Neither of the two glycans tested reduced HAdV-5 binding to or infection of SH-SY5Y cells (Fig. 3B and D). Based on these results, we conclude that HAdV-52 virions show a clear preference for polySia-expressing cells over cells lacking polySia, that the interactions with polySia are mediated by the 52SFK.

**PolySia Is Engaged at the Nonreducing End, Similarly to Monosialylated and Disialylated Glycans.** Using 2-α-L-methyl-sialic acid as a ligand, we previously identified a sialic acid-binding site on the lateral side of 52SFK (23). This binding site includes a stretch of three adjacent residues that together form a prominent RGN motif (R316–G317–N318). This site is located on a different part of the knob from the binding site of 37FK, which engages sialic acid near its threefold axis. The features responsible for the increased affinity for polySia are unknown, and it seems plausible that additional contacts or an additional epitope that went undetected in earlier studies are formed between 52SFK and polySia. Consequently, we solved the complex crystal structures of 52SFK with three oligoSia glycans (DP3, -4, or -5) as well as the GD3 glycan (Neu3NAc2,8Neu5NAc2,3Galp1,4Glc, representing a disialic acid motif). All complex structures produced similar results, as shown exemplary for DP3 in Fig. 4. Surprisingly, well-defined electron density was found only for a single sialic acid moiety in the canonical binding pocket in all cases. The electron density around O8 and its direction relative to the protein clearly indicate that it is the nonreducing end of the glycan chain that is engaged, and the observed binding mode is identical to the one observed for monosialic acid. In all cases except for GD3, we observed additional electron density for a second sialic acid moiety projecting from the pocket toward the solvent. The overall density for this moiety is weaker, deteriorating from the glycerol group to the pyranose ring and indicating increased flexibility. All structures showed similar angles for the α-2,8-glycosidic linkage (Fig. S2).}

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**Fig. 2.** HAdV-52 SFK binds to polySia. (A) HAdV FK binding to immobilized *E. coli*-derived polySia (colominic acid, DP ∼ 80–100). Relative absorbance is shown. (B) Flow cytometry-based quantification of HAdV FK binding to human neuroblastoma cells expressing (SH-SY5Y) or lacking (SK-N-SH) polySia. (C) Flow cytometry-based quantification of 52SFK and 37FK binding to SH-SY5Y cells after FK preincubation with increasing concentrations of pentasialic acid (DP5), FK, fiber knob; LFK, long fiber knob; SFK, short fiber knob. All experiments were performed three times with duplicate samples in each experiment. Error bars represent mean ± SD. **P < 0.01; ***P < 0.001.
contribute any direct contacts in the overall interaction, except for a van der Waals contact between its N-acetyl group and E328. This contact seems to cause a local decrease of electron density and a slight rotation of the N-acetyl group. The third (and all following) sialic acids could not be unambiguously traced in any of the structures. To verify our observations in solution, we performed saturation transfer difference (STD)–NMR spectroscopy to screen for glycan protons of DP3 and DP5 that are consistently placed within 5–6 Å of the protein (shown exemplary for DP3 in Fig. 4B and C). The spectrum of the glycans alone compared well with the literature (52, 53). Since all of the sialic acid repeats were in a highly similar chemical environment in solution, the respective peaks overlap—with the exception of the nonreducing end, which experiences an upfield shift. The experiment showed saturation transfer occurring almost exclusively at the nonreducing end, while the other moieties received only a very moderate spin saturation occurring exclusively in the N-acetyl group region, which is consistent with the contacts observed in the crystal structures. In the case of the R316A mutant, which disrupts the canonical RGN motif and prevents 52SFK attachment to sialic acid on A549 cells (23), saturation transfer was completely abrogated. Together, these results demonstrate that 52SFK engages polySia exclusively via its canonical sialic acid binding site, without any additional binding sites on the knob domain.

Transient Hydrogen Bonds and Electrostatic Effects Are Major Determinants of 52SFK:PolySia Interactions. A length of more than three sialic acid residues is required for a strong interaction with 52SFK, as seen in our glycan array data (Fig. 1). According to a cell attachment inhibition experiment, which does not underlie the steric constraints of chip-bound probes, a DP of 3 was sufficient to substantially decrease 52SFK binding at low concentration in solution. A decrease was also observed with DP2, but only at higher concentrations (Fig. 5A). Similar results were acquired from surface plasmon resonance experiments with immobilized FKs and oligoSia in solution, where the biggest increase in affinity was shown between DP2 and DP3 (Fig. 5B). In combination with the structural data, these findings suggest that effects other than classical directed short-range contacts account for the increased binding affinity of higher-order polySia compounds of DP3 or more. Given the polyanionic character of polySia, we hypothesized that these effects might be caused by

Fig. 3. OligoSia efficiently reduces HAdV-52 virion binding to and infection of SH-SY5Y cells. Binding of (A) 35S-labeled HAdV-52 and (B) 35S-labeled HAdV-5 virions to SH-SY5Y cells after preincubation with soluble monosialic acid (DP1) or pentasialic acid (DP5). Infection of SH-SY5Y with (C) HAdV-52 and (D) HAdV-5 after preincubation with DP1 or DP5. The experiments were performed three times with duplicate samples in each experiment. Error bars represent mean ± SD. *P < 0.05; ***P < 0.001.
electrostatic interactions, which are nondirected and can occur over longer distances than direct interactions such as hydrogen bonds or van der Waals contacts. Indeed, an inspection of the electrostatic potential of the 52SFK revealed a positively charged rim located around the sialic acid binding site, which we termed the “steering rim.” The rim is mainly formed by residues Q320, R321, R316, and K349 (Fig. 6 A–D). According to in-solution NMR studies, the polyanionic polySia seems to at least transiently adopt a left-handed helical conformation (54). However, polySia is expected to be rather flexible in solution due to its linear, nonbranched structure and the conformationally less restricted α-2,8-glycosidic linkage (42). In the DP3 complex structure, the second sialic acid moiety is positioned above the ε-amino group of K349. We reasoned that if the polySia glycan roughly followed the left-handed helical arrangement proposed in the literature with energy-minimal glycosidic torsion angles similar to those observed between the first two moieties (Fig. S2), the carbohydrate chain would protrude away from the protein surface into the bulk solvent (indicated in Fig. 6 E). Since such an arrangement is unlikely to enhance the affinity for polySia, we performed an MD simulation of the complex between 52SFK and DP5 on the microsecond timescale in explicit solvent. Throughout this simulation, DP5 shows a flexible structure with dynamic partial helical features (Movie S1). Consistent with the results from our STD-NMR experiments, only the nonreducing end is stably associated with the protein (Figs. 6 E and 7 A and B). However, the simulation shows that the other sialic acid residues transiently approach the protein surface and form favorable contacts with a variety of amino acids, most of which are located in the steering rim and the closely adjacent R347 (Fig. 7 A–D).

Fig. 4. α-2,8-Linked oligoSias are engaged in the canonical binding pocket of HAdV-52 SFK via their nonreducing end. (A) Complex structure of 52SFK and trisialic acid (DP3). Shown is a 2Fo – Fc map calculated at 1σ (blue) and 1.5σ (orange) after refinement. The nonreducing sialic acid moiety is colored in yellow, and the adjacent moiety in green. The third sialic acid moiety could not be resolved. (B) Schematic representation of sialic acid in the α-conformation. The positions of distinctive protons for NMR are indicated. (C) STD-NMR of 52SFK and DP3. Green box, DP3 alone; blue box, STD spectrum of the 52SFK:DP3 complex; red box, STD spectrum of the R316A-52SFK:DP3 complex; nr, nonreducing end.
While the sialic acid moieties adjacent to the nonreducing end mainly interact with a subset of residues located in the canonical pocket and steering rim, the moieties toward the reducing end show a much more variable interaction pattern with low occupancies for individual contacts. In total, however, the large majority of contacts are being formed with the canonical pocket or steering rim, respectively. The dimensions of DP5 are similar to those of DP4 and DP3, whereas the dimensions of DP6 are most of the time at least two pyranoses that directly interact with the protein (Fig. 7B). In fact, the lateral part of the knob is typically used for protein interfaces, for example, for CAR or CD46 (56). However, since the two fibers of HAdV-52 display a clear division of labor, the 52SFK likely serves as a purely Sia-binding FK and thus can accommodate conditions more weakly with polySia than R316 and K349 do, which fits well with the assumption of a flexible “pseudohelical” arrangement.

The PolySia Binding Site and the Steering Rim Are Conserved in Closely Related Simian Adenoviruses. The polySia-binding RGN motif is conserved in the short fibers of other closely related members of species HAdV-G: simian adenovirus (SAdV)-1, -2, -7, and -11, as well as SAdV-19 (SAdV-C), which acquired its short fiber from an unknown type/species (55), but it is not found in any other known nonhuman or human AdV, including the SFKs of HAdV-40 and -41 (HAdV-F) (Fig. S4A). Interestingly, the three positively charged residues forming the steering rim are also functionally conserved in these SAdV types, but in different permutations (RRK, RKK, RRR) (Fig. S4A). Another functionally important residue is Q320, which aids in the production of an electropositive field in the steering rim and is functionally conserved in all of the SAdV types of HAdV-G (but not in SAdV-19). No other HAdV FK with known structure exhibits a comparable steering rim (Fig. S4B). In fact, the lateral part of the knob is typically used for protein interfaces, for example, for CAR or CD46 (56). However, since the two fibers of HAdV-52 display a clear division of labor, the 52SFK likely serves as a purely Sia-binding FK and thus can accommodate conditions more weakly with polySia than R316 and K349 do, which fits well with the assumption of a flexible “pseudohelical” arrangement.

Discussion

We show here that HAdV-52 specifically engages cell surface-expressed polySia via its SFK, employing long-lived direct protein–carbohydrate contacts as well as transient longer-range electrostatic steering forces. With this study, we have identified an additional role of polySia, as a cellular receptor for a human
pathogenic virus. Although a growing number of polySia-binding proteins have been identified (58–64), there are relatively few in-depth structural analyses on the determinants of specificity for polySia, and to date no other polySia-binding protein has been reported to use the unusual binding mode presented here. We therefore believe that our analysis provides a useful framework for a better understanding of general aspects of the interactions of polySia with its binding partners, and it remains to be seen whether polySia reacts with other binding partners in a manner similar to that predicted for HAdV-52.

PolySia was identified as a potential receptor for 52SFK by glycan microarray screening (Fig. 1). In that same array, 52SFK

Fig. 6. Representation of the HAdV-52 SFK steering rim. Poisson–Boltzmann electrostatic potential isosurfaces and field lines for the protein were calculated at ±1, ±0.75, and ±0.5 kT/e. The positively charged rim can be seen in blue. Bound trisialic acid (DP3) is shown as green sticks. (A) Side view. (B) Top view including field lines. (C) Detailed view of the binding pocket including field lines. (D) Detailed view of the binding pocket showing the relative placement of glycan and steering rim residues. Residues of the steering rim are highlighted as sticks. R321 and E348 are forming a salt bridge, as do R316 and the carboxyl group at the nonreducing end of DP3. The orientation is the same as in A. (E) Side view of the interaction site. The second sialic acid moiety is projecting away from the protein surface. The green arrow indicates the expected direction of the adjacent sialic acid moieties. (D and E) The nonreducing sialic acid moiety is colored in yellow, and the adjacent moiety in green.
Fig. 7. MD simulation of the interactions between 52SFK and DPS. Three pentasialic acid (DPS) molecules interacting with the three identical binding pockets of 52SFK were simulated over a time of 2 μs. (A and B) The interaction profile of DPS with the protein is mapped onto 52SFK in a "heat map" style. Non-interacting residues are colored in gray, and interacting residues are scored from white (few interactions) to brown (strongly interacting). (A) All three pockets are shown from a top view. (B) One of the simulated binding pockets is shown from a side view. (C and D) Detailed interactions contributed by the additional sialic acid moieties in polySia. Amino acids of the canonical binding site are boxed in pink, and residues of the steering rim in orange. (C) Residue-residue interaction matrix showing the average number of favorable atom contacts between individual amino acids and sialic acids (SIA 2–5, counted from the nonreducing end) over the whole simulation. (D) Analogous plot showing the average number of hydrogen bonds. (E) Time-resolved trajectory plot of the number of atom contacts per sialic acid residue (numbered from the nonreducing end) in the three binding sites (individual rows) averaged over 2.5-ns increments. Atom contacts are counted as favorable if one of the following conditions are satisfied: H-bond donor/acceptor atom distance <3.2 Å or C-C atom distance of <4.2 Å. The average number of interactions is depicted according to the color legends on the Right for each panel. (F) Summary of the interactions of polySia with the 52SFK canonical pocket and steering rim. The number of favorable atom contacts and hydrogen bonds per residue is averaged over the three binding sites. Boxing of the amino acid residues is analogous to C and D; sialic acids are boxed in gray. (G) Flow cytometry-based analysis of HAdV-52 SFK mutant binding to polySia-expressing SH-SYSY cells. The experiment was performed three times with duplicate samples in each experiment. Error bars represent mean ± SD.
showed weaker binding to a number of glycans with single capping sialic acids, mainly \(\alpha\)-2,3-linked, as we described in our previous study (23). In a cellular context, however, blocking or removing \(\alpha\)-2,3-linked sialic acids from the cell surface had only a minor effect on HAdV-52 attachment (23). Thus, in comparison, polySia is a more effective ligand. The topology of the polySia binding site of HAdV-52 allows it to maintain a large pool of glycans and while developing increased affinity for a specific subset of surface molecules using just a single binding site. S25FK can engage differently linked sialylated glycans, which bind with their terminal, nonreducing sialic acid moieties to the same epitope using identical direct contacts. The strong preference for \(\alpha\)-2,8-linked polySia compounds is generated through a multitude of transient contacts between residues surrounding the binding site and sialic acid residues that are distal to the non-reducing end of the polySia chain. These transient contacts ensure that most of the time at least two Sia moieties are simultaneously associated with the protein, providing an avidity effect. In this manner, monosialylated and disialylated glycans are still able to interact with the knob with lower affinities, but could form the basis for a viable alternative strategy for developing oncolytic vectors, especially in the light of its low sero-prevalence rates and reduced liver tropism (23, 70). The specificity for polySia can also be increased further by mutating K349 to an arginine (Fig. 7G). With this in mind, we suggest that HAdV-52-based vectors could have a potential for treatment of cancers characterized by elevated polySia expression.

**Materials and Methods**

Please see SI Materials and Methods for information regarding cells, viruses, and glycans used in the study, and for detailed descriptions of production of fiber knobs, glycan microarray, ELISA, flow cytometry, virus binding and infection experiments, STD-NMR, crystallization, surface plasmon resonance, MD simulations, and statistical analysis.

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