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Structures of the Major Capsid Proteins of the Human Karolinska Institutet and Washington University Polyomaviruses

Ursula Neu, Jianbo Wang,† Dennis Macejak,2 Robert L. Garcea,2 and Thilo Stehle1,3*

Interfaculty Institute of Biochemistry, University of Tuebingen, Hoppe-Seyler-Str. 4, D-72076 Tuebingen, Germany1; Department of Molecular, Cellular, and Developmental Biology, University of Colorado at Boulder, 347 UCB, Boulder, Colorado 803092; and Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee 372323

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The Karolinska Institutet and Washington University polyomaviruses (KIPyV and WUPyV, respectively) are recently discovered human viruses that infect the respiratory tract. Although they have not yet been linked to disease, they are prevalent in populations worldwide, with initial infection occurring in early childhood. Polyomavirus capsids consist of 72 pentamers of the major capsid protein viral protein 1 (VP1), which determines antigenicity and receptor specificity. The WUPyV and KIPyV VP1 proteins are distant in evolution from VP1 proteins of known structure such as simian virus 40 or murine polyomavirus. We present here the crystal structures of unassembled recombinant WUPyV and KIPyV VP1 pentamers at resolutions of 2.9 and 2.55 Å, respectively. The WUPyV and KIPyV VP1 core structures fold into the same β-sandwich that is a hallmark of all polyomavirus VP1 proteins crystallized to date. However, differences in sequence translate into profoundly different surface loop structures in KIPyV and WUPyV VP1 proteins. Such loop structures have not been observed for other polyomaviruses, and they provide initial clues about the possible interactions of these viruses with cell surface receptors.

The human Karolinska Institutet polyomavirus (KIPyV) and Washington University polyomavirus (WUPyV) were discovered in 2007 (2, 9). Their closest relatives among polyomaviruses are the newly discovered human polyomaviruses 6 and 7 (HPyV6 and HPyV7, respectively) (21). They are also related to simian virus 40 (SV40), murine polyomavirus (Polyoma), and the human viruses BK (BKV), JC (JCV), Merkel cell polyomavirus (MCPyV) (8), Trichodysplasia spinulosa-associated polyomavirus (TSPyV) (28), and HPyV9 (22).

KIPyV and WUPyV have been identified in populations worldwide (reviewed in reference 11). Kean et al. (14) reported that 55 and 69% of (Western) adults are seropositive for KIPyV and WUPyV, respectively, with seroconversion occurring during childhood. Both viruses were sequenced from respiratory tract samples, indicating that they might persist in the respiratory system. However, they have not yet been linked to disease.

The architecture of polyomavirus particles is known from X-ray crystal structures of SV40 and Polyoma virions (16, 26). Their icosahedral capsids consist of 360 copies of the major structural protein viral protein 1 (VP1), arranged in 72 pentamers conforming to a T = 7d lattice. The core portion of VP1 adopts a β-sandwich fold with jelly-roll topology and assembles into stable ring-shaped pentamers. The N and C termini of VP1 form extensions that both emanate from the bottom of the pentamer, which corresponds to the inside of the capsid. The C-terminal extensions, termed “arms,” extend toward other pentamers in the capsid and contact them by adding a strand to one sheet of their β-sandwich cores. Each incoming C-terminal arm interacts with the N-terminal extension of the invaded VP1 monomer, which fastens the added strand, and then turns toward the interior of the virion to contact the viral DNA. These interactions are stabilized by Ca2+ ions. The surface of VP1 is formed almost entirely by extensive loops linking the β-strands of the core. These loops, the most variable regions of VP1, contain the receptor binding sites in other polyomaviruses and define the antigenicity of the virus (19, 20, 26).

The VP1 proteins of WUPyV and KIPyV share high sequence homology with each other but are much less similar to other polyomavirus VP1 proteins (21, 28). Since there is also high sequence homology among other polyomavirus VP1 proteins, the diverging WUPyV and KIPyV VP1 sequences point to a distant evolutionary relationship and perhaps an early evolutionary divergence from the polyomavirus family tree. It is thus likely that WUPyV and KIPyV possess structural features not present in other polyomaviruses that might provide insight into their receptor binding specificities.

In order to visualize these features, we have determined the crystal structures of the KIPyV and WUPyV VP1 proteins as pentameric capsomers. Despite their low sequence homology to VP1 proteins of known structure, the core structures of WUPyV and KIPyV VP1 are highly similar to those of other polyomavirus VP1 proteins. Interestingly, however, the surface loops of KIPyV and WUPyV VP1 have conformations that differ profoundly from those seen in other VP1 structures. Since these loops mediate receptor interactions in several polyomaviruses, their unique structures provide insights into the possible interactions of WUPyV and KIPyV with cell surface receptors.

* Corresponding author. Mailing address: Interfaculty Institute of Biochemistry, University of Tuebingen, Hoppe-Seyler-Str. 4, D-72076 Tuebingen, Germany. Phone: 49-7071-2973043; Fax: 49-7071-295565; E-mail: thilo.stehle@uni-tuebingen.de.
† Present address: College of Life Science, Capital Normal University, Beijing 100048, China.
‡ Published ahead of print on 4 May 2011.
TABLE 1. Crystallographic statistics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>KIPyV</th>
<th>WUPyV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit cell axes (a, b, c) (Å)</td>
<td>70.3</td>
<td>82.8</td>
</tr>
<tr>
<td>Unit cell angles (α, β, γ) (°)</td>
<td>90.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Resolution (Å)</td>
<td>50–2.55 (2.62–2.55)</td>
<td>40–2.9 (2.98–2.90)</td>
</tr>
<tr>
<td>No. of reflections (total)</td>
<td>237,505 (16,282)</td>
<td>159,898 (10,139)</td>
</tr>
<tr>
<td>No. of reflections (unique)</td>
<td>93,982 (6,639)</td>
<td>39,647 (2,908)</td>
</tr>
<tr>
<td>Completeness (%)</td>
<td>95.9 (91.1)</td>
<td>98.8 (99.4)</td>
</tr>
<tr>
<td>Rmerge (%)</td>
<td>5.4 (60.2)</td>
<td>9.6 (57.8)</td>
</tr>
<tr>
<td>Rwork (%)</td>
<td>95.9 (91.1)</td>
<td>98.8 (99.4)</td>
</tr>
<tr>
<td>Rmerge (%)</td>
<td>22.7 (34.5)</td>
<td>22.2 (33.0)</td>
</tr>
<tr>
<td>Rwork (%)</td>
<td>24.4 (36.7)</td>
<td>25.0 (35.7)</td>
</tr>
<tr>
<td>RMSD bond length (Å)</td>
<td>0.009</td>
<td>0.009</td>
</tr>
<tr>
<td>RMSD bond angle (°)</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>No. of protein atoms</td>
<td>19,845</td>
<td>9,966</td>
</tr>
<tr>
<td>Avg B factor (Å²)</td>
<td>56.2</td>
<td>58.0</td>
</tr>
<tr>
<td>B factor (Wilson) (Å²)</td>
<td>60.6</td>
<td>58.3</td>
</tr>
</tbody>
</table>

\[ \text{R}_{\text{merge}} = \sum |I_hkl| - |I_{hkl}'|/\sum |I_{hkl}|, \text{ where } I \text{ is the intensity of a reflection hkl, and} \text{<I>}_{hkl} = \text{the average over symmetry-related observations of hkl.} \]

\[ \text{R}_{\text{work}} = \sum |F_{hkl}| - |F_{hkl}'|/\sum |F_{hkl}|, \text{ where } F_{hkl} \text{ and } F_{hkl}' \text{ are the observed and calculated structure factors, respectively.} \]

\[ 5.0 \text{ and } 7.5\% \text{ of the reflections were not used during refinement to calculate free } R \text{ factors for the KIPyV and WUPyV models, respectively.} \]

RESULTS

Overall structure of KIPyV and WUPyV VP1. In order to crystallize the KIPyV and WUPyV VP1 pentamers, we recombinantly expressed truncated versions of each protein, spanning amino acids 31 to 303 of KIPyV VP1 and amino acids 33 to 295 of WUPyV VP1. The expression constructs were designed based on the constructs previously used for the crystallization of SV40 and Polyoma VP1 pentamers (20, 25). In all cases, the VP1 sequences contain the predicted β-sandwich core and form pentamers but cannot assemble into viral capsids due to truncation of their C-terminal arm. The N-terminal extension was deleted because it had inhibited crystallization of Polyoma VP1 (25) and only forms an ordered structure when the C-terminal arm is present. The structures of KIPyV and WUPyV VP1 pentamers were solved at 2.55- and 2.9-Å resolution, respectively (Fig. 1A and B; Table 1). Similar to other polyomavirus VP1 proteins, both KIPyV and WUPyV VP1 adopt the antiparallel β-sandwich fold iconic for viral capsid proteins. β-Strands are named alphabetically from the N terminus. Two β-sheets, formed by strands B, I, D, and G and strands C, H, E, and F, respectively. Two N-terminal extensions were also identified aligning with the most C-terminal part of the G strand and contacts the residues at the C terminus of the β-sandwich structure. In both KIPyV and WUPyV VP1, the β-sandwich structures are decorated with extensive loops that link the β-strands and make up most of the protein surface. The top surface of the pentamer, corresponding to the outer surface of the virion, is to a large extent formed by the long BC loop, which is divided for clarity into BC1 and BC2 loops (residues 59 to 70 and 77 to 90, in WUPyV, respectively, and residues 57 to 74 and 81 to 99 in KIPyV, respectively) that face in different directions (Fig. 1C). The sides of the pentamers are decorated with the extensive EF loops, parts of which fold into small, three-stranded β-sheets (Fig. 1). The CD loops at the bottom of each pentamer are disordered in most VP1 monomers and only become ordered when engaged in crystal contacts (Fig. 1C). They have elevated temperature factors, assume different conformations, and are poorly defined by electron density in all VP1 pentamer structures determined thus far (19, 20, 25). They also have variable conformations in structures of entire virions (16, 23, 24, 26).

The structures of WUPyV and KIPyV VP1 are highly similar to one another. The Ca atoms of a monomer of KIPyV and WUPyV VP1 can be superimposed with a low root mean square deviation (RMSD) value of 0.79 Å (Table 2), a finding consistent with their high sequence identity of 67.8%. The
N termini of the free pentamers forms the short Anew-strand, WUPyV and KIPyV VP1, a short stretch of amino acids at the very well onto each other (Table 2). The structure of the –sandwich core is conserved among WUPyV-KIPyV VP1 pentamers was first determined, it was unclear whether the Anew-strand conformation observed in free pentamers was relevant or not. Since the free pentamer structures of the rather diverse polyomaviruses Polyoma, SV40, WUPyV and KIPyV that all belong to different space groups all feature an Anew-strand, it is much more likely that this conformation is a common feature of free pentamers and has physiological importance. One possible function of the Anew-strand might be to contact the beginning of the C-terminal arm of the same monomer and to guide it away from the molecule to prevent self-invasion (25).

Comparison with other polyomavirus VP1 structures. Multiple sequence alignment and phylogenetic analysis revealed that VP1 proteins from all polyomaviruses known to date can be classified into three main phylogenetic groups (21, 28): (i) one comprising SV40 and the related BKV and JCV; (ii) a large and diverse group containing Polyoma, as well as MCPyV and avian polyomaviruses; and (iii) a third group that is more distant in evolution and consists of WUPyV, KIPyV, and the newly discovered human viruses HPyV6 and HPyV7.

We therefore compared the KIPyV and WUPyV VP1 structures to two structurally known members of the other two groups, SV40 and Polyoma VP1, by superposing structures of unassembled pentamers of each protein using different residue ranges and calculating RMSD values for their Cα atoms (Table 2). The monomer superpositions for the different proteins were then manually combined into a structure-based sequence alignment (Fig. 2). For reference, the SV40-JCV VP1 pair was also included (19) because these two VP1 proteins feature a high level of sequence identity of 77% in the truncated pentamers used here.

The structure of the β-sandwich core is conserved among all proteins compared (Table 2). The β-sandwich cores of WUPyV and KIPyV VP1 superimpose very well onto each other (RMSD = 0.42 Å). However, they both differ significantly from the core structures of SV40 and Polyoma VP1, as

### TABLE 2. Comparison of WUPyV, KIPyV, SV40, Polyoma, and JCV VP1 structures

<table>
<thead>
<tr>
<th>Structure comparison</th>
<th>Co RMSD (Å)</th>
<th>Monomer (core only)</th>
<th>Monomer</th>
<th>Pentamer</th>
</tr>
</thead>
<tbody>
<tr>
<td>WUPyV-KIPyV</td>
<td>0.42</td>
<td>0.79</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Polyoma-KIPyV</td>
<td>0.72</td>
<td>1.57</td>
<td>1.98</td>
<td></td>
</tr>
<tr>
<td>SV40-KIPyV</td>
<td>0.76</td>
<td>1.48</td>
<td>1.90</td>
<td></td>
</tr>
<tr>
<td>SV40-Polyoma</td>
<td>0.46</td>
<td>1.11</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td>SV40-JCV</td>
<td>0.34</td>
<td>0.71</td>
<td>0.86</td>
<td></td>
</tr>
</tbody>
</table>

a VP1 monomers or unassembled VP1 pentamers of WUPyV, KIPyV, SV40 (pdb 3BWR [20]), Polyoma (PDB IVP5 [25]), and JCV VP1 (PDB 3NXD [19]) were superimposed on one another with Superpose in CCP4 (4) using a secondary-structure matching algorithm. Conserved core structures were identified from the structure-based sequence alignment of WUPyV, KIPyV, SV40, and Polyoma as stretches of sequence with more than 5 amino acids, for which the average RMSD of the KIPyV-SV40, KIPyV-Polyoma, and Polyoma-SV40 pairs was <0.8 Å. For SV40, these were amino acids 44 to 55, 86 to 92, 109 to 120, 144 to 166, 193 to 199, 202 to 227, 232 to 254, 257 to 269, 277 to 282, and 283 to 295. These were then superposed by using LSQMAN (15).
evidenced by elevated RMSD values for the KIPyV-SV40 and KIPyV-Polyoma comparisons. These structural differences are more pronounced when entire monomers, including the diverse loops, are compared. The RMSDs for entire pentamers are even higher than for monomers when WUPyV or KIPyV are compared to SV40 or Polyoma. This indicates that the orientation of monomers with respect to one another is somewhat different within the WUPyV and KIPyV VP1 pentamers compared to the SV40 and Polyoma structures. Taken together, our analysis supports the conclusion that the VP1 proteins of KIPyV and WUPyV form a new group that is different from both the group represented by Polyoma and the group represented by SV40 (Table 2). The structural comparisons are also consistent with the structure-based sequence alignment (Fig. 2), which reveals larger differences in sequences among SV40, Polyoma, WUPyV, and KIPyV VP1 than between WUPyV and KIPyV VP1 alone.

**FIG. 2.** Structure-based sequence alignment of WUPyV, KIPyV, Polyoma, and SV40 VP1. Protein regions for which all structures align with RMSD values between Ca atoms that are <0.8 Å and with RMSD values between Ca atoms that are <1.5 Å are colored blue and light blue, respectively. Regions in which only the WUPyV and KIPyV structures align with each other are colored orange and yellow for Ca RMSD values of <0.8 and <1.5 Å, respectively. Regions in which only SV40 and Polyoma align with each other are colored purple and light purple for the same Ca RMSD values. β-Strands are indicated with gray arrows. Residues shown in lowercase letters and colored gray were not included in the expression constructs and are therefore not present in the crystal structures. Every tenth amino acid in each sequence is highlighted in boldface.

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and E residue and inserted into the EF loop is structurally well conserved between all four viruses (Fig. 2).

**Structure of the BC loop.** The BC1 loop of KIPyV is six amino acids longer than the BC1 loop of WUPyV VP1. Most of these additional residues are disordered in all 10 copies of KIPyV VP1 in the crystal structure, suggesting that they are also flexible in solution. However, the N- and C-terminal parts of the WUPyV and KIPyV BC1 loops are conserved and feature the same conformation, which is stabilized by interactions between residues at the beginning and end of the BC1 loop (Fig. 3H). Most prominent is the conserved π-stacking interaction between N59, H72, and W74 in KIPyV VP1 (N61, H68, and W70 in WUPyV VP1). The asparagine and histidine residues in this sequence are further stabilized by conserved hydrogen bonds to main chain atoms.

Subtle differences in other parts of the protein likely serve to accommodate the different BC1 loop conformations of WUPyV and KIPyV compared to their SV40 and Polyoma counterparts. For instance, the BC1 loop conformation observed in WUPyV and KIPyV would clash with the main chain of the EF loops of SV40 and Polyoma, which are one amino acid longer.

The BC2 loops of both WUPyV and KIPyV VP1 are stabilized by salt bridges that link the beginning and the end of the...
loop and by main-chain hydrogen bonds to the EF loop (Fig. 3F and G). The long protrusions in the BC2 loop of KIPyV are rather flexible, as indicated by elevated B factors, but they adopt the same structure in the eight chains in the asymmetric unit that are completely defined by electron density (Fig. 3F). BC-linker. Although both the BC1 and BC2 loops assume different conformations in the WUPyV (green), KIPyV (purple), Polyoma (dark gray), SV40 (light gray), and JCV (medium gray) VP1. The structures were superposed using only the six residues of the linker with LSQMAN (15). The backbone atoms of the BC-linkers and of the three preceding and following residues are shown as thin lines. The side chains of the BC-linker residues are shown in stick representation and labeled according to the consensus sequence of the linker. The Co atoms of the glycines often found as first residue of the linker are indicated as spheres. (C) Interactions of the BC-linker of KIPyV VP1. The Co traces of the BC-linker and the I’ strand of KIPyV are shown in ribbon representation and colored purple. The main chain is shown as lines, and side chains engaging in contacts are shown in stick representation. Side chains are colored as in panel A. Nitrogen atoms are colored blue and oxygen atoms are colored red.

Features of the virion surface. The surface loops of the KIPyV and WUPyV VP1 structures differ substantially in their conformations from those seen in other polyomaviruses. Since these loops constitute the bulk of the surface-exposed area of the virus, they are primarily responsible for the appearance of the virion surface (Fig. 5). The BC1 loops of KIPyV and WUPyV form large protrusions at positions on the top and side surfaces of VP1 that differ in location from protrusions observed in SV40 and Polyoma. On the other hand, the HI loops of WUPyV and KIPyV VP1 are six amino acids shorter than their counterparts in SV40 or Polyoma. Consequently,
they do not protrude as far from the capsid, instead forming a groove between other, longer loops (Fig. 3A and D, Fig. 5C and D). The long, protruding BC2 loops of KIPyV VP1 render its surface especially rugged, contributing to the formation of a deep groove that has not been observed in any other polyomavirus VP1 structure (Fig. 5A and C).

**DISCUSSION**

We have determined the structures of the VP1 pentamers of two newly identified polyomaviruses, KIPyV and WUPyV. Based on their sequences, these two viruses are evolutionarily distant from other polyomaviruses. Consistent with this divergence, the two new structures hold some surprises and reveal novel features that had not been seen in other polyomaviruses. These features provide insights into possible modes of receptor engagement by KIPyV and WUPyV, and they also provide a platform for understanding essential features of the very recently described HPyV6 and HPyV7 viruses.

The receptors used by KIPyV and WUPyV are still unknown. However, inspection of the unique surface structures of the KIPyV and WUPyV VP1 pentamers provides insights into what types of receptors they might bind. Structural analyses have defined how the VP1 proteins of SV40, JCV, and Polyoma engage their receptors, which in all cases terminate in sialylated oligosaccharides (19, 20, 25, 27). The mode of interaction with sialic acid is conserved in SV40 and JCV, whereas...
Polyoma binds sialic acid in a different orientation and with different residues (19, 20, 25). However, none of the sialic-acid binding residues of SV40, JCV, or Polyoma are conserved in the WUPyV and KIPyV VP1 structures. In addition, the BC1 loops, which are involved in sialic acid binding in Polyoma and SV40, point into a different direction in KIPyV and WUPyV (Fig. 3 and 5). Moreover, the residues at the tip of the HI loop that contact the oligosaccharides in the SV40 and Polyoma complexes are not present in WUPyV and KIPyV VP1, and their HI loops are also much shorter. This configuration leads to surprisingly different surface structures of KIPyV and WUPyV compared to SV40 and Polyoma (Fig. 5). Whereas SV40 and Polyoma feature a wall formed by the tip of the HI loop at the back of the oligosaccharide binding site, KIPyV and WUPyV feature a groove at that position of the surface (Fig. 5C to F). We therefore believe it unlikely that KIPyV or WUPyV bind sialic acid in a manner similar to that seen in SV40, JCV, or Polyoma VP1.

It is possible that KIPyV and WUPyV bind sialic acid in a new orientation or at a different location. We note that MCPyV, which also lacks the residues that contact sialic acid in Polyoma, SV40, and JCV, has been shown to bind sialylated oligosaccharides (7), and thus there is precedent for an alternative ligand binding pocket and/or orientation in VP1 pentamers. It is also possible that KIPyV and WUPyV do not bind sialic acid at all, perhaps engaging other carbohydrates or even proteinaceous receptors. The unique structural features of the WUPyV and KIPyV VP1 pentamers provide some support for this second possibility.

Both KIPyV and WUPyV VP1 feature pronounced grooves on the top surface of VP1, which might be involved in receptor binding (Fig. 5C and D). These grooves are deeper than the shallow depressions that bind oligosaccharides in SV40 and Polyoma VP1 (Fig. 5E and F). In KIPyV VP1, the groove is flanked by the protruding BC2 loops on each side (Fig. 5C). This rugged surface might serve to accommodate a peptide receptor or a very long oligosaccharide chain. Interestingly, the electron density map for WUPyV VP1 revealed similar electron density features in the grooves of all five VP1 monomers that can best be explained by bound glycerol molecules (Fig. 5D). Glycerol is included in the cryoprotectant solution in high concentrations. Since it has three adjacent hydroxyl groups, glycerol mimics part of a monosaccharide and is even present in sialic acid. The glycerol binds near a positively charged patch on the surface of WUPyV VP1 that is formed by residues of the HI and BC2cw loops. Thus, the presence of glycerol might point to an oligosaccharide binding site, perhaps a negatively charged oligosaccharide such as a sulfated glycosaminoglycan or a sialylated oligosaccharide. We note that heparin is also a receptor for the related papillomaviruses (10, 12). Unfortunately, the structural data presented here allow few conclusions concerning specific receptor binding until the nature of their receptors are identified by other means.

The structures of WUPyV and KIPyV VP1 also shed light on likely features of the VP1 structures of the newly identified human papillomaviruses HPyV6 and HPyV7, which share homology with WUPyV and KIPyV VP1 but are more distantly related to other polyomavirus VP1 proteins (21). The HPyV6 and HPyV7 viruses likely also contain a BC-linker that anchors the endpoints of the BC1 and BC2 loops, although sequence alignments in this region are somewhat ambiguous. It is clear, however, that the BC loops of HPyV6 and HPyV7 are much shorter than their KIPyV and WUPyV counterparts, and thus unlikely to form similar protrusions. On the other hand, the HI loop sequences of HPyV6 and HPyV7 VP1 are much longer than those of all other polyomaviruses and may perhaps even fold back onto the VP1 core structure. Taken together, the surfaces of HPyV6 and HPyV7 likely have protrusions and recessions that are quite different from those seen in other polyomaviruses. The KIPyV and WUPyV VP1 structures reported here thus highlight the capacity of the conserved pentameric VP1 core to support highly diverse loop arrangements, which endow the different polyomaviruses with unique interaction surfaces.

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ADDITIONAL INFORMATION

After the manuscript was accepted, the international Committee on Taxonomy of Viruses (ICTV) created the genus Wikipolyomavirus, thus taking into account the evolutionary distance of WUPyV and KIPyV from other polyomaviruses.

REFERENCES