Atomic Structure of Human Adenovirus by Cryo-EM Reveals Interactions Among Protein Networks

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Construction of a complex virus may involve a hierarchy of assembly elements. Here, we report the structure of the whole human adenovirus virion at 3.6 angstroms resolution by cryo-electron microscopy (cryo-EM), revealing in situ atomic models of three minor capsid proteins (IIIa, VIII, and IX), extensions of the penton base and hexon major capsid proteins, and interactions within three protein-protein networks. One network is mediated by protein IIIa at the vertices, within group-of-six (GOS) tiles—a penton base and its five surrounding hexons. Another is mediated by ropes (protein IX) that lash hexons together to form group-of-nine (GON) tiles and bind GONs to GONS. The third, mediated by IIIa and VIII, binds each GOS to five surrounding GONS. Optimization of adenovirus for cancer and gene therapy could target these networks.

Human adenovirus (Ad) causes acute respiratory, gastrointestinal, and ocular infections, as well as fulminant infections among children and immunocompromised individuals, and engineered versions are used for gene therapy and vaccines against cancer and other diseases (1–4). It is among the largest (~920 Å diameter) and most complex (~150 megadaltons) of the nonenveloped double-stranded DNA (dsDNA) viruses (5). Its icosahedral capsid shell (Fig. 1) is composed of three major proteins: 240 hexon trimers (“hexons”), each in the shape of a hexagon; 12 penton-base pentamers (“penton base”), each in the shape of a pentagon; 12 penton base–associated fiber trimers (“fibers”); and four minor proteins (IIIA, VIA, VII, and IX) (table S1) (5–7). The genome core inside the capsid is composed of the DNA; five additional proteins (V, VII, µ, Va2, and terminal protein); and viral protease (8). We sought to characterize the logic and details of the interactions responsible for assembly and stabilization of the virion.

Crystal structures (~3 Å) are available for the isolated hexon (9, 10), penton base (11, 12), and fiber (12). Cryo–electron microscopy (cryo-EM) structures are available for the intact virion (7, 13–17)—including the minor proteins VIII and IIIa on the inner surface of the capsid and IX on the outer surface—but at a resolution (6 Å) (15) that does not permit characterization of interactions among the proteins. Here, we report a 3.6 Å resolution structure of human adenovirus type 5 (Ad5) by cryo-EM single-particle analysis, that enabled us to construct atomic models for these three minor proteins and to resolve critical regions of the hexon and penton base not seen by x-ray crystallography. These models reveal networks of interactions mediated by minor proteins IIIa, VIII, and IX that stabilize two large systems of tiles—one on each facet of a group of nine (GON) capsomers (6, 18–20) and at each vertex a group of six (GOS) capsomers—and hold those tiles together.

Overall structure of the virion. We reconstructed the three-dimensional structure (density map) of Ad5 (Fig. 1A and movies S1 and S2) from 31,815 individual particle images in 1350 films using the IMIRS software package (21, 22). The effective resolution of our structure, 3.6 Å, is estimated by the reference-based Fourier shell correlation coefficient (23) (fig. S1). Representative α-helix density map (Fig. 1C and movie S3) and β-strand density maps (fig. S2 and movie S4) from the hexon protein (movie S5) are consistent with this estimate.

The 240 quasi-equivalent hexons are classified as H1, H2, H3, and H4, according to their location within each facet of the pseudo T = 25 icosahedral capsid (6) (Fig. 1B). The 12 penton bases are centered on the 12 vertices of the icosahedron (Fig. 1, A and B), and each of the 12 fiber trimers associates with a penton base. The densities of hexons, penton bases, fibers, and the four minor proteins (IIIA, VIII, VI, and IX) are individually colored in Fig. 1B and movie S2. Minor protein IX is included in the outer surface (Fig. 1B, top) of the capsid—not on the outer surface itself but halfway down the hexon (15, 16) (side view in the top left inset of Fig. 1B). By contrast, minor proteins IIIa and VIII sit on the inner surface (Fig. 1B, bottom) underneath the inner boundaries of penton bases and hexons (side view in the bottom right inset of Fig. 1B) (15). Protein VI is also located beneath hexons, as indicated by previous cryo-EM structures, in a cavity on the inner surface of each hexon (15, 24). Our result is consistent with this observation, but perhaps due to random occupancy (~360 copies among 720 hexon monomers), the cryo-EM density is weak. The copy numbers and resolved amino acids of these capsid proteins are summarized in table S1.

Protein IIIa. Monomers of protein IIIa (red in Fig. 2A), underneath the penton base and peripental (H1) hexons, are arranged around the fivefold axis (Fig. 2A). We resolve the structure of amino acids 7 to 300 of protein IIIa.

**References**

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The remainder of the protein (amino acids 301 to 585) is not visible, which implies flexibility. The resolved structure is predominantly helical (Fig. 2B), with only one three-stranded \( \beta \) sheet (fig. S3). It has the shape of a seahorse (Fig. 2B and movie S6) and can be divided into four domains according to their interactions with other proteins (Fig. 2B). We can visualize densities associated with the side chains of \(~85\%\) of the amino acids (fig. S3), but not all of these densities are sufficiently distinctive for us to identify amino acids. Therefore, we use amino acids that are large and distinctive (table S2) as “landmarks” to obtain accurate registration of amino acids in our atomic model. Construction of the protein IIIa atomic model allows us to describe interactions with other proteins by identifying amino acids with a visible density at the site of side-chain contacts ([22]; proposed details of nine sites of interactions in table S3A). For example, the GOS-glue domain, the tail of the seahorse, interacts with a penton-base monomer (Fig. 2A, right, bottom inset), an adjacent protein IIIa (same inset), and two peripentonal hexons, thus binding the penton base to neighboring peripentonal hexons. The VIII-binding domain, the neck of the seahorse, interacts with protein VIII (Fig. 2A, right, top inset) to bind peripentonal hexons to hexons farther away.

**Protein VIII.** Monomers of protein VIII, also located on the inner capsid surface, are arranged around both fivefold and threefold axes (Fig. 2A). Each monomer is organized into an extended conformation with three domains: head, neck, and body (Fig. 2C). Our density map and the resulting model of the head domain are in good agreement with previous mass spectrometry data showing that protein VIII is cleaved at two positions during viral maturation, G110 and R159 (25), (Fig. 2C, inset), which causes the middle segment (amino acids 111 to 158) to be shed from the mature capsid (26). As with protein IIIa, we can visualize densities associated with the side chains of \(~85\%\) of the amino acids (fig. S4), and we use bulky amino acids (table S2) as landmarks to build our atomic model (fig. S4 and movie S7). Similarly, we identify 13 sites of interactions—each characterized by visible densities at the sites of side-chain contacts—for each protein VIII with other proteins ([22]; proposed details on interactions in table S3B). For example, every copy of protein VIII interacts with four hexons, two on either side of its body, one to the side of its neck, and one to the side of its head (Fig. 2A, center). The large body domain includes three antiparallel \( \beta \) strands that interact with protein IIIa (Fig. 2A, top right inset). In addition, each of the \( \beta \) strands in the head and body domains joins the \( \beta \) sheets of the VC region of two hexons via \( \beta \)-strand augmentation (Fig. 2A, top insets).

**Protein IX.** The protein IX network is best viewed from the outside (multicolored in Fig. 3A, center). Each monomer (Fig. 3B) has an N-terminal domain (~30 Å long), a rope domain (~70 Å), and a helix-bundle domain with a long 12-turn helix (~65 Å), all joined by loops. We could visualize the densities of side chains of \(~85\%\) of the amino acids in the N-terminal domain and \(~70\%\) in the helix-bundle domain (fig. S5, A and B). As above, we use bulky amino acids (table S2) as landmarks to obtain accurate registration of amino acids in our atomic model for these two domains. In addition, we describe protein IX’s interactions with other proteins by identifying either visible densities at the sites of side-chain contacts (for the N-terminal and helix-bundle domains) or by close proximity (for the rope domains) ([22]; proposed details of six sites of interactions in table S3C).

At the N terminus of three protein IX monomers, the N-joint regions (Fig. 3B, blue) form a trimERIC joint (Fig. 3A, top left inset; fig. S5C; and movie S8). The three contributing monomers radiate from this joint, shown as either three yellow monomers or a red, a green, and a blue (Fig. 3A, center). Four of these N-joints are located in each facet, one at the threefold axis (yellow in Fig. 3A) and three at local threefold axes (each with red, green, and blue monomers in Fig. 3A). The N-joint is tied by a hydrophobic core that includes three tyrosines and three leucines (Fig. 3A, top insets).

At the C terminus of protein IX, four helix-bundle domains coil together to form a ~65 Å long four-helix bundle (Fig. 3A, right insets; fig. S5D; and movie S9). These four-helix bundles, three in each facet, are centered on three local two-fold positions inside the three edges of a facet. The amino acid sequence in the helix-bundle domain of protein IX shows a heptad-repeat motif with the hydrophobic Leu in the \( d \) position (leucine zipper: L100, L107, L114, and L121), typical of a helix bundle. Indeed, there are additional hydrophobic leucines and valines in the helix-bundle domain, specifically L103, L110, V117, L124, V128, and L131 (table S4).

Three of the helices (blue, yellow, and green) of a four-helix bundle come from the same facet of the capsid and traverse the same distance, two hexagon edges (each ~60 Å), before joining at the base of the bundle (center of Fig. 3A; see also the section “Interaction networks” below). These would run in parallel with each other. However, the fourth helix (red) comes from a neighboring facet, reaches the tip of the helix bundle after traversing the standard two hexagon edges, joins the bundle there, and continues to the base of the helix bundle (black arrows in fig. S5, E and F). Inspired by figure 4 in (15), this arrangement, with the red helix running antiparallel to the other three, was already demonstrated by use of peptide-tagged recombinant protein IX (27).

Identification of amino acid side chains among the four helices (fig. S5D, table S2) and visualization of the densities of the rope domains of the four proteins IX in an asymmetric unit (movie S10) confirm this unusual arrangement, with three

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**Fig. 1.** Overall structure of the Ad5 capsid. (A) Radially colored surface of a reconstruction of the capsid, centered on a threefold axis. (B) Views of the outer surface (top) showing minor protein IX—and, following rotation—the inner surface (bottom) of a facet showing minor proteins IIIa, VI, and VIII. All hexons, penton bases, and penton fibers are shown semitransparently except for one hexon monomer (+) and one penton-base monomer (−). (Top left inset) Side view of protein IX among hexons. (Bottom right inset) Side view of proteins IIIa and VIII centered on a penton base. (C) Atomic model (sticks) of an \( \alpha \) helix from a hexon monomer superimposed on its density map (mesh) with some side chains labeled.
parallel helices and one antiparallel helix. Indeed, the hydrophobic leucines and valines listed above create a ladder of hydrophobic interactions between these parallel and antiparallel helix-bundle domains (table S4) to create a hydrophobic core (Fig. 3A, right insets). This arrangement would tack down both ends of the helix bundle and hold the bundle rigidly in place, which may explain why the helix bundle is well resolved in structural studies.

Although filtering to low resolution reveals all of the parts of all four copies of protein IX (fig. S5, E and F, and movie S10), our high-resolution structure shows clearly the entirety of just the blue copy (fig. S5, A and B). Therefore, we use flexible fitting of the blue rope domain to model the green, yellow, and red rope domains in the center of Fig. 3A. Even for the blue copy, amino acid registration for the rope domain is uncertain because of the relatively low density of that domain (fig. S5, A and E). With that caution in mind, we have nonetheless built an atomic model of all three domains of the blue copy of protein IX. For the red, green, and yellow copies, we have built atomic models of only their N-terminal and helix-bundle domains.

**Major capsid proteins and conformational adaptability.** Derived from the cryo-EM density map of the whole virion, our atomic models of the penton-base and hexon proteins (Fig. 4, A and B; red ribbons) are in excellent agreement with those from x-ray crystallography (9–11). However, our models reveal features not seen in the crystal structures, as well as many in situ interactions absent from crystal structures of isolated proteins. For example, at the N terminus of each penton-base monomer, we see amino acids 37 to 51 (blue “N-arm” in Fig. 4A). This string of amino acids interacts with two adjacent IIIa proteins (Fig. 2A, bottom right inset; model and densities in fig. S6; and table S3A) and then turns inward to connect with the genome core, all of which anchors the penton base.

We also see an N-terminal extension (amino acids 2 to 7) and a C-terminal extension (amino acids 944 to 950) of the hexon. With four types of hexon (H1 to H4) in an asymmetric unit, there are 12 hexon monomers (fig. S7A), but depending on the location of the subunit and adapting to its interaction with neighboring proteins (see legend of Fig. 4C), the N-terminal extension (Fig. 4C) shows just five different conformations for its short stretch of amino acids. Some of these conformations interact with minor proteins IIIa and VIII on the inner surface (tables S3, A and B), others with neither. Likewise, the C-terminal extension (amino acids 944 to 950 in Fig. 4D and fig. S8A) shows different conformations, six in this case. The first three, like the C-terminal extension type a (fig. S8B), interact with protein VIII; the last three do not.

In addition, at the top of the hexon in our cryo-EM model, we see four loops (amino acids 251 to 256, 271 to 278, 431 to 436, 443 to 444) (Fig. 4B, blue ribbons and labels). The first three are within the hypervariable regions HVR4, HVR5, and HVR7 that are important for typing-specific immunogenicity (10). The one loop (amino acids 251 to 256) in the H4 hexon monomer (fig. S5E) interacts with the tip of the four-helix bundle of protein IX and anchors the latter in the valley between two hexons.

Finally, our 3.6 Å resolution structure shows the amino acids involved in hexon-hexon and hexon-penton base interactions by revealing amino acid residues that are within 7 Å distance (fig. S7 and proposed details of interactions in table S5). Because of the scarcity of visible side-chain contact densities, we suggest that these interactions are generally weaker (like the one shown in fig. S7B) than those between the major and minor proteins. Although these interactions cannot be seen in the crystal structures of the individual proteins, they are largely in agreement with predictions based on fitting the crystal structures to these proteins in their native packing, as revealed in 10 Å cryo-EM maps of the whole virion [table 1 in (14)].

**Interactions with the genome core.** Our map also revealed interactions of two kinds between capsid shell proteins and the genome core, indicating a role for capsid proteins in genome packaging. The first kind is the N-arm of the penton base, extending to the genome core (fig. S9, A to C), consistent with the report that the penton base can bind core protein V (27). The second kind is a density underneath and near protein IIIa (fig. S9D), which looks like a rod at low resolution and has the characteristic features of a helix at high resolution. According to its site and copy number, 60 per virion, this rod density is likely to be part of

![Fig. 2. Interactions among minor and major proteins on the inner surface.](image)
the C terminus of protein IIIa, consistent with the ability of protein IIIa also to bind core protein V (17, 29).

Prior reports show that protein VI binds hexons (30) and core protein V (31) and that its C terminus activates the virion protease that cleaves multiple precursor proteins, required for virion maturation and infectivity (32). We find protein VI in the cavity on the underside of the hexon, consistent with these observations.

**Interaction networks among minor and major proteins.** Using detergent, Smith *et al.* (18) obtained dissociation fragments that became known as GONs—groups of nine (20) hexons—one in each of the 20 facets (6). Following that example, we call the one penton base pentamer and its five peripentonal hexons a GOS—a group of six capsomers—each centered on a vertex (Fig. 5A schematic).

As shown in the sphere in Fig. 2A and in the Fig. 5A schematic, five copies of protein IIIa monomer (red) on the inner surface of the capsid form a network centered on a penton base. This network appears to hold together the penton base and peripentonal hexons to form a GOS, with many contacts between penton base and peripentonal hexons and between peripentonal-hexon neighbors (Fig. S10A and table S3A).

From the network point of view, the protein VIII molecule (blue) on the inner surface of the capsid has three kinds of interactions (Fig. 5A schematic, fig. S10A, and table S3B). First, its head and neck domains bind neighboring hexons within each GON. Second, its body domain binds neighboring GONs to each other at a local twofold position (i.e., the SS interface between H3 and H2 hexons in fig. S7A). Third, its body domain joins GON hexons and GOS hexons at another local twofold position (i.e., the SS interface between H4 and H1 hexons in fig. S7A).

Indeed, the last type of interaction appears to be the main interaction between GON and GOS tiles.

Protein IX on the outer surface of the capsid forms a network that lines the boundaries between hexons, bonds extensively with them, lashes them together into GONs, and binds GONs to GONs (Fig. 5B). Coextensive with GONs, protein IX essentially avoids GOS tiles, with only one monomer—the red one—having just one interaction site with H1 hexon protein (no. 5 in table S3C). Detergent treatment dissociates adenovirus into GONs and GOS capsomers (18). We suppose that this dissociation is the result of disruption of the hydrophobic cores within the three four-helix bundles situated at local twofold positions (TT interfaces between H2 and H4 hexons in fig. S7A) at the edges of each GON (Fig. 5B and table S5). Moreover, dissociation of a protein IX–deletion mutant virus produces isolated hexon and penton-base capsomers but no GONS (32).

The schematic (Fig. 5B) also illustrates the argument that the yellow, blue, and green protein IX monomers traverse two hexagon edges before reaching the base of the four-helix bundle, whereas the red monomer traverses two hexagon edges before reaching the tip of the four-helix bundle. The blue protein IX monomer extends along the sides of just one hexon (H4), whereas the others must be more flexible in crossing the valley between two different hexons, which may explain why the density of the blue one is best resolved. Indeed, the four monomers take different combinations of turns at the beginning and at the end of their rope domain; specifically, the parallel blue turns left and left, the parallel yellow turns right and left, the parallel green turns left and right in Fig. 5B, consistent with the diagram in figure 4D of (15), and the antiparallel red from the neighboring GON turns left and left. In addition, the green helix domain crosses over the other three and interacts with a hexon (H4) (Fig. 5B and table S3C).

**Discussion.** Many dsDNA viruses, including some bacteriophages and herpesviruses, assemble a protein capsid first, followed by motor-driven insertion of genomic DNA through a portal complex at one of the 12 vertices into the preformed capsid (34, 35). Indeed, a recent study suggests the presence in adenovirus of a homolog of the bacteriophage portal protein (36). Moreover, empty
capsid particles and normal-size particles with a fraction of the normal DNA have been detected (37). Therefore, the size of the virion is likely to be determined by its capsid components, probably the assembly of GON and GOS tiles, which depend primarily on interactions between major and minor proteins (Fig. 5). For example, in the absence of protein IX—which may act like the “tape-measure” protein P30 in bacteriophage PRD1 (38, 39)—the adenovirus virion can accommodate a slightly larger than normal genome (40).

If the protein IX network, with several domains that are tied at both ends—the N-joint at one and the four-helix bundle at the other—is under tension, its elastic cables working in opposition to the outward force from the core stuffed with enough DNA (41) may be essential to the stability of the virus. Indeed, adenovirus without protein IX has poor thermostability (33).

Our atomic structures have enabled us to identify the amino acids responsible for interactions among the minor and major proteins in the virion (tables S3 to S5). By genetic engineering, these amino acids could be systematically manipulated to generate more stable, less stable, or temperature-sensitive particles, and conceivably, larger capsids. Such larger capsids might permit an increase in the payload of genes carried by an engineered adenovirus for cancer and gene therapy. In addition, our atomic model of the whole virion has revealed which amino acids of protein IX, the hexon, and the penton-base are exposed on the outer surface. These amino acids could serve as targets for genetic engineering to modulate tissue targeting (41). Finally, insofar as adenovirus causes illness, especially among young children and immunocompromised adults, it should be possible to rationally design drugs to target those binding sites.

Fig. 4. Newly resolved regions in penton-base and hexon proteins. (A) Cryo-EM model (ribbons) of the penton-base protein superimposed on its density map (semitransparent gray). Outside the box, the cryo-EM atomic model (red ribbons) is identical to the x-ray model (11). Inside the box is our newly resolved N-arm (blue ribbon, amino acids 37 to 51). (Inset) Enlargement of the boxed region, showing side-chain densities (mesh) and its atomic model (ribbon). (B) Cryo-EM model of the hexon protein. Red ribbons show agreement with the x-ray model (10). Blue ribbons show our newly resolved pieces, including the N-terminal and C-terminal extensions. Region names in the hexon monomer (e.g., VC and FG) follow (10). (C to D) Conformational adaptation. (C) Twelve hexon monomers exhibit five types of N-terminal extension in an asymmetric unit: four of type 1, two each of types 2 and 3, one of type 4, and three of type 5. (D) Twelve hexon monomers exhibit six types of C-terminal extension: two each of types a, b, c, and d, three of type e, and one of type f. Ribbon models superimposed on density (mesh) of these six types are shown in fig. S8A.

Fig. 5. Schematic illustrations of interactions among minor and major proteins. Interactions are marked here, numbered in fig. S10, and listed in table S3. (A) Contacts on the inner surface of the capsid. Letters a to f denote the positions of six types of hexon C-extensions. At each vertex, five copies of protein IIIa link five peripentonal hexon trimers and a penton-base pentamer to make a GOS tile (light blue shading). Protein VIII mediates binding among hexons, links GON tiles (gray shading) to GON tiles, and links GON tiles to GOS tiles. (B) Contacts on the outer surface among the four types of hexon trimer (H1, H2, H3, and H4) and the four types of protein IX monomer (red, green, yellow, and blue) that are inlaid into the canyons at the borders between hexons. Protein IX lashes hexons together to form GON tiles and also links GON tiles.
Strange Metal Transport Realized by Gauge/Gravity Duality

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Fermi liquid theory explains the thermodynamic and transport properties of most metals. The so-called non-Fermi liquids deviate from these expectations and include exotic systems such as Fermi liquid theory explains the thermodynamic and transport properties of most metals. The so-called non-Fermi liquids deviate from these expectations and include exotic systems such as Fermi liquid theory explains the thermodynamic and transport properties of most metals. The so-called non-Fermi liquids deviate from these expectations and include exotic systems such as Fermi liquid theory explains the thermodynamic and transport properties of most metals. The so-called non-Fermi liquids deviate from these expectations and include exotic systems such as Fermi liquid theory explains the thermodynamic and transport properties of most metals. The so-called non-Fermi liquids deviate from these expectations and include exotic systems such as Fermi liquid theory explains the thermodynamic and transport properties of most metals. The so-called non-Fermi liquids deviate from these expectations and include exotic systems such as

During the past decade, developments in string theory have revealed surprising and profound connections between gravity and many-body systems, resulting in the emergence of a new description for strongly coupled many-body systems. The anti-de-Sitter/conformal field theory (AdS/CFT) correspondence (1–3) relates a gravity theory in a weakly curved (d + 1)-dimensional anti-de Sitter (AdS_d+1) spacetime to a strongly coupled d-dimensional quantum field theory defined on its boundary. This correspondence maps questions about complicated many-body phenomena at strong coupling to solvable single-or few-body classical problems in a curved geometry. Black holes in this geometry play a surprising and universal role in characterizing the dynamics of the boundary theory at finite temperature and density, a development anticipated by the discovery of Hawking and Bekenstein in the 1970s (4, 5) that black holes are intrinsically thermodynamic objects. Important dynamical insight into the thermodynamics (6) and transport behavior (7) of strongly correlated systems has been obtained from simple geometric aspects of black hole spacetimes.

Very recently, this apparatus has been brought to bear on the problem of fermions near quantum criticality (8–11). The basic strategy is to perform angle-resolved photoemission (ARPES) thought experiments on a charged black hole, which describes the ground state of a class of strongly coupled many-body systems. The fermionic response, which is proportional to the ARPES intensity, may be computed by studying the scattering of Dirac particles off this black hole. By exploring different regions in parameter space, both Fermi liquid–like (10) and non–Fermi-liquid behavior (9, 11) were discovered, establishing the black hole as a new tool for addressing outstanding questions related to interacting fermions at finite density.

A prime example of a theoretical challenge to which such a tool may be applied is the strange metal phase of the cuprate high-temperature superconductors. The metallic state above the superconducting transition temperature Tc near optimal doping has unusual transport properties different from those of a normal metal, and was thus dubbed a strange metal; understanding this phase is believed to be essential for deciphering the mechanism for high-Tc superconductivity. The anomalous behavior of the strange metal (perhaps most prominently the simple and robust linear temperature dependence of the resistivity) implies that the low-