Structural Comparisons of Empty and Full Cytoplasmic Polyhedrosis Virus

PROTEIN-RNA INTERACTIONS AND IMPLICATIONS FOR ENDOGENOUS RNA TRANSCRIPTION MECHANISM*

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Viruses in the family Reoviridae are capable of transcription within the intact capsids. As the only single-shelled and thus the simplest member of the Reoviridae, cytoplasmic polyhedrosis virus (CPV) provides an attractive system for studying endogenous transcription. We report the structures of the full and empty CPV determined at 13 Å resolution by electron cryomicroscopy. The structure of the empty CPV reveals a density attributed to the transcription enzyme complex, which is attached to the internal surface of the capsid shell below each of the 12 turrets. The full capsid has an identical capsid shell but contains additional internal densities contributed by the genomic double-stranded (ds) RNA. The RNA densities proximal to the capsid shell are organized into layers with a dodecahedral appearance, suggesting a genome organization of dsRNA segments each having a cone shape spooling around a transcription enzyme complex. Our structures also suggest that the capsid shell serves as a scaffold for appropriate positioning of the RNA genome, whereas nascent mRNA release takes place through the constricted central channel of the turret. Based on these observations, a detailed moving template transcription mechanism is proposed that may provide insight into the well coordinated and highly efficient endogenous RNA transcription of dsRNA viruses.

CPV† is one of the most widespread insect pathogens and belongs to the cytopogenus of the Reoviridae family (1). Viruses in the Reoviridae are distinctive as they all have a segmented dsRNA genome that is transcribed within intact capsids (2). Nascent mRNA is capped before being released from the intact capsid. The mechanism by which this characteristic endogenous transcription takes place inside intact dsRNA viruses has been studied extensively (3–7), and it is generally believed that the RNA polymerase complex is structurally anchored to the core during transcription (7–9). The dsRNA template must be flexible enough to move freely within the densely packed core so that it can slide through the RNA-dependent RNA polymerase (RDRP) and the capping enzyme complex to ensure efficient transcription (10). However, the detailed mechanisms for achieving this efficient endogenous transcription, the control of dsRNA movement, and its interaction with the RDRP during this process remain unclear.

Unlike the double-shelled (e.g. rice dwarf virus) or triple-shelled viruses (e.g. animal reovirus) that are typical in the Reoviridae family, infectious CPV has only a single capsid shell and is thus the structurally simplest member of the Reoviridae (11, 12). This single protein capsid, made up of five structural proteins with 12 turret-like projections, encompasses a dsRNA genome of 10 segments. Despite this striking difference in the outer shell organizations, viruses in the Reoviridae share a common core structure within which the RDRP and dsRNA segments are organized into physically and functionally separate units, suggesting a common dsRNA genome packaging pattern and mechanism of RNA transcription (13). The genes encoding RDRP that catalyzes the endogenous transcription are conserved among different dsRNA viruses (14). Therefore, as the simplest member of the Reoviridae family, CPV provides an attractive model system for studying the structural and functional organization of endogenous transcription.

Both x-ray crystallography and electron cryomicroscopy (cryo-EM) have been employed to study the three-dimensional structures of dsRNA viruses. In particular, the crystal structure of the animal reovirus core (15), which is structurally homologous to CPV, and that of the bluetongue virus sub-core (7, 16) have provided detailed descriptions of the structural and functional organizations of shell proteins. Yet due to the unavailability of the crystalline structures of empty capsids, the interactions of RNA/protein (both TEC and shell protein) cannot be discerned directly in either case. Moreover, at atomic resolution, the RNA densities cannot be optimally resolved due to the lack of icosahedral symmetry at such resolution. Conversely, the high quality of cryo-EM data particularly in the resolution range of 10–30 Å facilitates resolving dsRNA genome densities and RNA-protein interactions by imaging both full and empty capsids for three-dimensional structure comparison. Previous 100-kv cryo-EM studies of CPV at ~25 Å resolution effectively illustrated the overall structural features of the capsids but failed to reveal sufficient structural information on genome organization or dsRNA-protein interactions (11, 12). Improvements in imaging by using a 400-kv cryo-EM in the current study have allowed us to substantially improve...
the resolution of full and empty CPV structures to 13 Å, thus enabling the direct visualization of the enclosed TEC and RNA genome structures in greater detail. We show that the dsRNA genome is organized into layers consisting of continuous coils of dsRNA bundles spaced ~27 Å apart and surrounding the TEC densities, which is consistent with a cone-shaped spooling organization of dsRNA duplexes spiraling around each TEC. These observations form the basis of our proposed mechanism that may explain the highly efficient and well orchestrated endogenous transcription of dsRNA viruses.

EXPERIMENTAL PROCEDURES

Purification and Cryo-EM of CPV—The full and empty particles were purified from the gut tissues of infected fifth-instar larvae of Dendrolimus spectabilis by differential centrifugation as described previously (11). The full and empty capsids were imaged together to permit a direct structural comparison of the particles recorded under the same condition. Focal pair micrographs of CPV capsids embedded in vitreous ice were taken in a 400-kV JEOL 4000 electron cryo-microscope at 50,000 magnification with an electron dose of about 12 electrons/Å² for each micrograph (17). The micrographs were digitized on a Zeiss microdensitometer (Z/I Imaging, Huntsville, AL) at a step size of 2.8 Å/pixel, and individual virus particles were extracted as images of 300 × 300 pixels.

Data Processing and Three-dimensional Reconstruction—The determination of the center and the orientation parameters of each boxed out particle and subsequent refinement were carried out using procedures based on Fourier common lines as described previously (18–20). The particles from the far-from-focus micrographs were used as an aid in the determination of the parameters of the particles in the close-to-focus micrographs (18). Prior to the merging of particle images for three-dimensional reconstruction of the full and empty capsids, respectively.

FIG. 1. Typical area of the close-to-focus (A, underfocus 0.8 µm) and far-from-focus micrograph (B, underfocus 3.3 µm) of a focal pair of 400-kV electron micrographs of ice-embedded CPV capsids. The filled and open arrows indicate a full and an empty CPV capsid, respectively.

FIG. 2. Structural comparisons of the full and empty capsids at 13-Å resolution. A and B, shaded surface views of the reconstructions of the full (A) and empty (B) capsid along 2-fold axes. The arrows point to a star-shaped constriction in the turret. C and D, central sections (~55-Å thick) from the maps of the full (C) and empty (D) capsid. Unless otherwise indicated, the maps in this and subsequent figures are color-coded according to particle radius such that the 12 turrets are in pink, the protrusions on the capsid layer in aquamarine, and the capsid layer in green. The internal densities (within a radius of 245 Å) in the full capsid are shown in red, and those in the empty capsid, attributed to the TEC, are shown in purple. C, the TEC densities extracted from the empty capsid are superimposed on the full capsid to reveal their relative radial locations. E, radial density distributions of the empty and full CPV reconstructions. The mass densities in the three-dimensional maps of the full (solid line) and empty (dotted line) capsids are spherically averaged and plotted as a function of particle radius. The radial positions of structural components in full and empty capsids are indicated.
RESULTS AND DISCUSSION

Three-dimensional Structural Comparisons between Full and Empty Capsids—Empty and full particles are visually distinguishable in the cryo-EM micrographs (Fig. 1). We merged particle images from a set of close-to-focus micrographs with different defocus values in order to obtain an even data sampling across a wide range of spatial frequencies. The reconstructions for the full and empty capsids were computed from 1100 and 774 individual particle images, respectively. The effective resolution of the empty capsid reconstruction is determined to be 13 Å based on the criterion of the Fourier shell correlation coefficient between two independent reconstructions being larger than 0.5. The map of the full particles was determined to a higher resolution and subsequently Fourier-filtered to the same resolution (13 Å) as that of the empty particles for structure comparison. Both the full and empty capsids show an almost identical icosahedral shell, each decorated by 12 characteristic turrets at icosahedral vertices, 120 square-shaped large protrusions, and 120 globular small protrusions (Fig. 2A and B). The turret has an open upper cavity above a star-shaped constriction (Fig. 2A and B, arrows). These structural features, although grossly similar to those revealed at 25 Å previously (11, 12), are now resolved with much greater detail, enabling the subsequent identification of protein-protein and RNA-protein interactions and structural comparison of the empty and full capsids.

Densities Attributed to the dsRNA Genome and TEC—The central slice of the full capsid shows strong internal densities organized into roughly spherical layers (Fig. 2C), which are not present in the central slice of the empty capsid (Fig. 2D). As the only chemical difference between the empty and the full capsid is the presence/absence of the RNA genome (11), we conclude that these layers of densities correspond to the RNA genome in the full capsid. Each mushroom-shaped density attached to the internal surface at the 5-fold axis of the empty capsid represents the contribution of one TEC (Fig. 2D) (11).

The RNA layer densities closer to the capsid layer are more
Fig. 4. Structures of proteins involved in transcription. A and B, side views of the region encompassing the turret and its underlying TEC associated with intertwining RNA densities from empty (A) and full (B) particles. C and D, three-dimensional structure of the 6β RDRP determined by x-ray crystallography (21) shown either at atomic resolution using ribbons (C) or Gaussian-filtered to 10-Å resolution and rendered as shaded surface representation, with the RNA-binding cleft indicated by an arrow (D). E, the 10-Å density map of 6β RDRP after aligning its RNA-binding cleft aligned along a 5-fold axis and imposing 5-fold symmetry. The 5-fold axis is perpendicular to the page. The arrow points to a central hole apparent after symmetrization. F, densities attributed to CPV TEC computationally extracted from the three-dimensional map with the 5-fold axis perpendicular to the page. The arrow points to a prominent central hole along the 5-fold axis. G, superposition of the CPV TEC and 6β RDRP as shown in D. The central hole of CPV TEC is aligned with the RNA-binding cleft, which is indicated by the arrow. H, superposition of E and F. Note their central holes match precisely (arrow). I, slightly tilted side view of the superposition of 6β RDRP as shown in E on the turret-TEC region of the empty CPV J, the same as I but the unsymmetrized 6β RDRP density as in D is shown. The maps were all displayed using a density contour level of 1.5σ except that in A, which is displayed at 0.5σ.

ordered than those close to the center of the capsid (Fig. 2C). The three layers closest to the capsid have continuous and well-organized densities. In addition, the RNA layers are not perfectly spherical but rather angular, having a shape similar to that of the surrounding capsid layer, except those below the turret where the RNA densities appear to be displaced inward. This displacement is most obvious in the third layer, possibly due to the presence of the bulk of the TEC. Thus, it seems that both the shell protein and TEC are important in maintaining the layer structure of the RNA genome, preventing it from expanding freely, which is energetically more favorable in the absence of protein constraints.

The difference between the density distributions in the full and empty capsids can also be illustrated by comparing their radial density distributions (Fig. 2E). The protein density distributions of the two capsids are almost identical as indicated by the good match of the spherically averaged radial density distributions beyond radius 230 Å, corresponding to the region of the capsid shell and spikes (Fig. 2E). However, only the full capsid has density peaks regularly spaced –27 Å apart within radius 230 Å, which correspond to densities of the RNA genome. The 27-Å spacing indicates that the CPV genome is more densely packed than that of BTV (7) but less densely packed than those of bacteriophages, which exhibit a spacing of 22–24 Å (22).

Previously, crystallography studies on the cores of animal reovirus and bluetongue virus have resolved their structures to atomic resolution (7, 15). However, due to the unavailability of the empty capsid structures at the same resolution, the genomic RNA densities and their interactions with viral proteins could not be unambiguously resolved. In this study, with both full and empty CPV capsids reconstructed to 13 Å, a difference map between the full and empty capsids representing only the contribution from the RNA density can thus be computed to provide a clear demarcation of RNA-protein interactions and shed further insights into the dsRNA organization (Fig. 3). The RNA densities are organized into concentric decahedral cages (Fig. 3A). The inner surface of the protein capsid imposes a high level of icosahedral order on nearby dsRNA by making numerous contacts on the first layer of RNA density around the 5- and 2-fold axes (Fig. 3B). Therefore, due to their interactions with the enclosing capsid shell, the outer layers of the RNA densities are arranged with a certain level of icosahedral symmetry, at least to the current resolution range of the reconstructions, even though no sequence repeats or homologies are present among the different segments of the RNA genome.

Around each pentagonal opening of the second shell of the decahedral shaped RNA density are two roughly continuous coils of RNA density bundles with an inter-bundle spacing of about 27 Å (Fig. 3D). In the first layer, similarly separated bundles of densities are also visible when displayed at a higher density contour level (not shown). The average diameter of each density bundle is about 20 Å, which is the same as the diameter of dsRNA duplex, suggesting that each density bundle revealed in these layers represents a dsRNA duplex. The TEC density is situated at the center of the dsRNA density coils and interacts with the surrounding RNA densities (Fig. 3E). It is conceivable that the coils in different RNA density layers surrounding the same TEC represent different portions of the same dsRNA segment. The linker joining these neighboring coils is invisible due to icosahedral symmetrization imposed during three-dimensional reconstruction.

Proteins Involved in mRNA Transcription and Post-transcriptional Processing—To closely examine the protein-RNA and protein-protein interactions contributing to the RNA transcription and processing steps, we segmented out regions around the icosahedral 5-fold axis encompassing the TEC, the turret, and its associated capsid shell densities from the empty and full maps. The TEC densities revealed in the empty capsid...
are weaker than the capsid shell densities. But when displayed at a lower density threshold (0.5σ), they appear tethered to the inner surface of the capsid shell (Fig. 4A). The weaker TEC density is expected as only one transcriptase is present below each 5-fold vertex, which was smeared out by 5-fold averaging imposed during three-dimensional reconstruction. From the side view of the densities surrounding the TEC, it is clear that the bulk of TEC is located below the turret between the first and third RNA layer (Fig. 4B). The genomic dsRNA molecules interact extensively with both the TEC and the capsid shell as can be identified from the side view of the full map (Fig. 4B).

RDRP has the highest level of conservation among proteins of dsRNA viruses, including CPV and the bacteriophage φ6 (14, 21, 23, 24). A recently determined atomic structure of the bacteriophage φ6 RDRP has revealed it as a globular right-hand-shaped protein composed of finger, thumb, and palm domains (Fig. 4C), with an overall fold similar to other RNA transcriptase from viruses such as the hepatitis C virus (21, 25). Therefore, we expect the CPV RDRP, the major protein constituent of TEC, to be globular also. Although the TEC densities are smeared out and thus difficult to interpret, some of its structural features may provide interesting clues about the functional organization of TEC inside the capsid. First, arm-like tethers are seen connecting the body of TEC to the capsid shell (Fig. 4, A and F), suggesting that either a large conformational change of the transcriptase or binding of additional proteins is necessary to form the arms from the globular transcriptase structure. Second, there is a hole with a diameter of about 8 Å in the TEC densities along the 5-fold axis on its side facing the capsid shell (Fig. 4F). Interestingly, when we oriented the φ6 RDRP (Fig. 4, C and D) with its RNA-binding cleft facing the capsid shell along the 5-fold axis and imposed 5-fold symmetrization on it, a hole of similar size can also be seen on the symmetrized density along the 5-fold axis facing the capsid shell (Fig. 4, E, H, and I). Therefore, we propose that the location of the hole on the TEC density corresponds to the RNA-binding cleft of the CPV TEC. With such an orientation, the C-terminal thumb domain of the RDRP is the closest to the capsid shell, making it a probable candidate to interact with the protruding densities of the capsid shell protein (Fig. 4J).

Studies of the turret protein of the animal reovirus core suggested that a central channel is used for mRNA release (15), whereas research on rotavirus implied one of the five peripheral channels as a possible candidate for the release pathway (4). Below the CPV turret, there is a small pore that can either be plugged or opened (26). This pore is closed in both the full and empty CPV capsids that are not undergoing active transcription. Our result of the RNA binding cleft on the TEC near the 5-fold axis (see above) lends support for a release pathway along the 5-fold axis, using the pore that can switch from an open to a sealed state under different chemical conditions (26). It is conceivable that this pore is closed when the CPV capsid is at a quiescent state and would become open by a conformational switch leading to the release of mRNA.

Model of RNA Organization and Implications for Transcription Mechanism—CPV has a dsRNA genome of about 25 kb, consisting of 10 dsRNA segments with length ranging from 0.94 to 4.19 kb (27–32). As estimated from our reconstruction, the entire genome must be packaged within a volume of \( \sim 6 \times 10^3 \) Å\(^3\), corresponding to a concentration of RNA of \(-500\) mg/ml

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within the core. It is possible that at this concentration the RNA is packed in a liquid crystalline state and thus can slide over each other with little constraint in the presence of positively charged small molecules such as spermidine or cations (34). The above-observed structure of RNA layers and the interactions between TEC and dsRNA have led us to propose a model of CPV genome organization (Fig. 5A), which extends from those proposed for the genomes in other Reoviridae members (7, 34). In this model, each dsRNA molecule spirals around the TEC down toward the center of the capsid like a layered cone-shaped spool with an inter-layer distance of 27 Å. The outmost layers are composed of multiple coils of RNA duplex with an inter-duplex spacing of 27 Å, although close to the center the dsRNA strand is in a less organized form. The strand is confined both laterally and radially by the steric hindrance due to the presence of adjacent RNA cones. Both ends of the dsRNA strand are attached to the TEC, as suggested by the observations that the segmented dsRNA functionally operates as circular templates during transcription (10, 35). The anchor-strands by TEC and then capped by the turret protein on its 3' end (39) and subsequent release of the newly synthesized mRNA strand from the turret. The ATP consumption during mRNA synthesis in CPV is greater than that calculated from ATP integrated into mRNA (33), suggesting that ATP may provide the energy needed for the movement of both template and nascent transcripts during this process. Due to space limitations near the center of the capsid, the stretched dsRNA strands are forced to coil upward. The clashing force with the neighboring dsRNA molecules with the other end of itself would lead to the upward coiling of the dsRNA eventually into a spiral shape (Fig. 5D). Upon completion of this round of transcription, the RNA molecule resumes the coiled spiral shape and enters into a new cycle, leading to a continuous, well orchestrated, and highly efficient RNA transcription process.

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