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Minireview

Structure, attachment and entry of polyoma- and papillomaviruses

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ABSTRACT

Polyoma- (PY) and Papillomavirus (PV) virions have remarkable structural equivalence although no discernable sequence similarities among the capsid proteins can be detected. Their similarities include the overall surface organization, the presence of 72 capsomeres composed of five molecules of the major capsid proteins, VP1 and L1, respectively, the structure of the core segment of capsomeres with classical antiparallel "jelly roll" β strands as the major feature, and the linkage of neighboring capsomeres by invading C-terminal arms. Differences include the size of surface exposed loops that contain the dominant neutralizing epitopes, the details of the intercapsomeric interactions, and the presence of 2 or 1 minor capsid proteins, respectively. These differences may affect the dramatic differences observed in receptor binding and internalization pathways utilized by these viruses, but as detailed later even structural differences cannot completely explain receptor and pathway usage. In recent years, technical advances aiding the study of entry processes have allowed the identification of novel endocytic compartments and an appreciation of the links between endocytic pathways that were previously thought to be completely separable. This review is intended to highlight recent advances in our understanding of virus receptor interactions and their consequences for endocytosis and intracellular trafficking.

Structure

Polyomaviruses

The outer shell of Polyomavirus (PY) virions is composed of 360 molecules of the major capsid protein VP1. They are organized into 72 capsomeres, each comprised of a pentameric VP1 assembly, centered on the vertices of a *T*=7 icosahedral lattice. Twelve and sixty capsomeres are pentavalent and hexavalent, i.e. they have five and six nearest neighbors, respectively. The core of the capsomeres is mainly composed of an antiparallel β-sandwich to which eight β strands labeled B through I contribute (Liddington et al., 1991; Stehle et al., 1996). They run roughly parallel to the 5-fold axis and are connected by small loops. The BC, DE, FG, and HI loops face outwards and contain the major neutralizing epitopes. The five VP1 molecules within a capsomere are intimately associated, even displaying an interlock of their secondary structures. The overall structure of the β-sandwich is identical in all capsomeres.

Neighboring capsomeres are linked by invading C-terminal arms, with each capsomere donating 5 arms and likewise receiving 5 arms from 5 neighboring capsomeres. These interactions are stabilized by Ca^{2+} ions and disulfide bonds. The interactions by the sequence elements inserting into the neighboring capsomeres (C insert; residues 315 to 344 in SV40 VP1) are the same for all VP1 molecules. The A β-strand and A α-helix of the receiving VP1 molecules provide a clamp which locks the J strand (residues 330 to 336) of the C insert into place. This interaction is further stabilized by residues 337 to 344, which wrap around the N-terminal arm and end at the Ca^{2+}-binding site (Li et al., 2003). The C-terminal arm also contains the C helix and the C loop, which are the most variable parts and differ in the three distinct kinds of capsomere–capsomere interactions. Three-fold clusters link one VP1 molecule from pentavalent capsomeres to two VP1 molecules donated by two neighboring hexavalent capsomeres such that C-terminal arms are exchanged in a cyclical fashion. Two different 2-fold clusters each contain two hexavalent capsomeres and are found at the icosahedral 3-fold and 2-fold axis, respectively. In SV40, this configuration brings the highly conserved cysteine residues at position 104 (C104) into close proximity allowing them to engage in disulfide bonds. In the three-fold clusters, one C104 remains reduced and is not involved in disulfide bond formation (Liddington et al., 1991). Recent evidence suggests that the cysteine residue at position 9 (C9), which was not visible in the X-ray structure, forms C9–C9 disulfide bonds and also contributes to intercapsomeric crosslinks between VP1 molecules (Schelhaas et al., 2007). Thus, essentially all VP1 molecules in the particle are covalently connected. In murine PY (PyV), such an extended cross-linking is not observed which may have consequences for the specific requirements of viral uncoating during entry (see below).

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In addition to VP1, 72 molecules of minor capsid proteins, VP2 and VP3, are present in the viral capsid. VP2 differs from VP3 by an N-terminal extension of 116 residues that carries a myristylation site (Gasparovic et al., 2006; Krauzewicz et al., 1990; Sahli et al., 1993). A highly conserved C-terminal fragment spanning residues 266 to 302 (VP2 numbering) inserts in a hairpin-like manner into the axial cavity of capsomeres present on the inner capsomere surface. Strong hydrophobic interactions with 3 of the 5 VP1 molecules anchor the VP2/VP3 molecules (Chen et al., 1998). Due to high flexibility no structural information could be obtained for other parts of VP2 but it is believed to be completely hidden inside the capsid and thus not accessible, e.g. to antibody binding (Norkin et al., 2002).

Papillomaviruses

Like the PY capsid, the outer shell of Papillomaviruses (PV) is composed of 360 molecules of the major capsid protein, L1 (Baker et al., 1991). The structural information for HPV16 was derived from $T=1$ capsids composed of only 12 pentamers. The core capsomere is very similar to the PY structure with eight β-strands contributing to the antiparallel β-sandwich (Chen et al., 2000) (Figs. 1A, B). The BC, DE, FG, and HI surface loops are considerably larger. The larger size of L1 as compared to VP1 explains size differences between the PY and PV capsids (50 nm as compared to 60 nm, respectively). This structural information suggested that the C-terminal arm folds back into the core

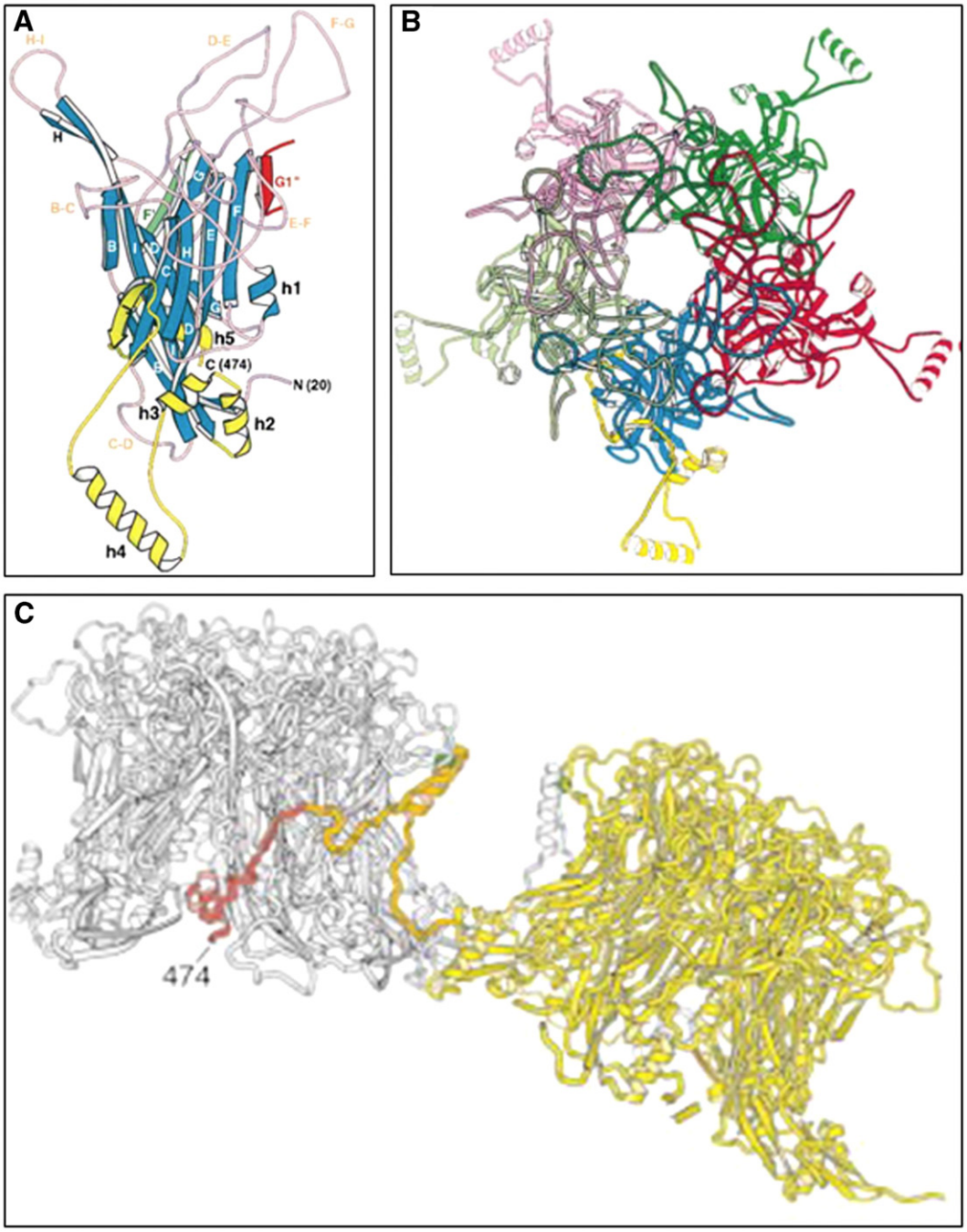

Fig. 1. Structure of HPV16 L1. (A) Structure of a L1 monomer. (B) L1 capsomere viewed along the five-fold axis. Both images were reproduced with permission from (Chen et al., 2000). (C) The invading arm model reproduced with permission from (Modis et al., 2002).