

REVIEW

Picornavirus uncoating

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Recently, much has been learned about the molecular mechanisms involved in the pathogenesis of picornaviruses. This has been accelerated by the solving of the crystal structures of many members of this virus family. However, one stage of the virus life cycle remains poorly understood: uncoating. How do these simple but efficient pathogens protect their RNA genomes with a stable protein shell and yet manage to uncoat this genome at precisely the right time during infection? The purpose of this article is to review the current state of knowledge and the most recent theories that attempt to answer this question. The review is based extensively on structural data but also makes reference to the wealth of biochemical information on the topic.

the icosahedral fivefold axis and its C-terminal close to the threefold axis. The N-terminal residue of VP4 in all picornaviruses is covalently bonded to a myristic acid group,⁸ giving the capsid five symmetry related myristoyl moieties around the inner surface of the icosahedral fivefold axis. At this point, a channel runs through the capsid connecting the inner and outer surfaces.

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It is the seemingly minor structural variations on this theme that result in the diverse range of infectious agents, with their equally diverse modes of uncoating, known as the family Picornaviridae.

The family Picornaviridae is comprised of small, icosahedral, non-enveloped viruses with a single positive strand RNA genome. Its members are among the smallest known human and animal pathogens. The family is classified into six genera: the human rhinoviruses (HRVs), which are the causative agents of many common cold infections; the enteroviruses, which include poliovirus and bovine enterovirus (BEV); the aphthoviruses, which include foot and mouth disease virus (FMDV); the cardiomyoviruses, including Mengo virus; the hepatomyoviruses, which include the causative agent of hepatitis A; and the parechoviruses, which are responsible for a wide range of human infections.

PICORNAVIRUS STRUCTURE

The picornavirus capsid, an approximately spherical structure of diameter 30 nm, is composed of 60 copies of each of four structural proteins VP1 to VP4¹ in icosahedral symmetry.^{2,3} The crystal structures of diverse representatives of the family have been solved.^{4,5} The fundamental capsid architecture is the same in all members. In each case, VP1, VP2, and VP3 are in the approximate range 240 to 290 residues, each taking the form of eight stranded antiparallel β sheet structures with a “jelly roll” topology. These proteins form the outer surface of the capsid (fig 1). The capsid shell varies in thickness but averages around 5 nm. In the case of enteroviruses and rhinoviruses, VP1 contains a cavity, or pocket, lined with hydrophobic residues and accessible from a depression on the outer surface of the virus capsid.^{2,6,7} VP4 is much shorter, around 70 residues, and is almost totally lacking in secondary structure. This protein lies across the inner surface of the capsid with its N-terminus close to

ATTACHMENT TO CELLS

The first stage of picornavirus infection of susceptible cells is mediated by the interaction of the viral capsid with specific receptors on the cell membrane. No structurally distinct virus capsid features that are common to all members of the picornavirus family have been implicated in this process. However, it is known that the receptor binding sites in the human rhinoviruses and certain members of the enteroviruses lie in a deep cleft at the base of a depression, or “canyon”, which surrounds each fivefold axis.² The residues in this cleft are both immunologically sequestered and highly conserved within virus groups. Although this may be true for rhinoviruses⁹ and enteroviruses such as poliovirus,⁶ some members of this genus, such as coxsackievirus A9 (CAV9)⁷ and bovine enterovirus,³ do not possess a canyon, merely depressions at analogous positions on the capsid. This is caused by extended loops from the outer capsid proteins filling the canyon at various points. In the case of CAV9 there is a C-terminal extension to VP1 (of 15 residues), which contains an arginine–glycine–aspartate (RGD) motif¹⁰ that is known to bind integrin molecules. In BEV there is an insertion relative to other enteroviruses of five residues in VP3, which forms a loop that has been implicated in receptor binding. The BEV capsid proteins do not contain the RGD tripeptide, indicating that this virus uses yet another attachment mechanism. Aphthoviruses, which lack any

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Abbreviations: BEV, bovine enterovirus; CAV9, coxsackievirus A9; FMDV, foot and mouth disease virus; HRV, human rhinovirus; RGD motif, arginine–glycine–aspartate; WIN, Winthrop



Figure 1 Structure of bovine enterovirus (BEV). The colour scheme is: VP1, blue; VP2, green; VP3, red; and VP4, yellow. Only the main chain folding pattern is shown for clarity.

appreciable surface depressions, do have an RGD motif in VP1, but in this case it is located in a long flexible surface loop,⁴ which is shared across all seven FMDV serotypes. Although the biochemistry of this attachment mechanism is apparently similar to that of CAV9, the FMDV case is unique among picornaviruses in that the attachment site is not only immunologically exposed but forms part of the major neutralising epitope.¹¹

This attachment phase is the determinant of tissue tropism. In spite of the fact that atomic resolution structures have been solved for representatives of four of the six genera, there is comparatively little known about the mechanism of receptor binding. To date, the only structural information is for a human rhinovirus complexed with a fragment of its receptor, intracellular cell adhesion molecule 1.¹² Cellular receptors for coxsackievirus and FMDV are known and all belong to the integrin family. The coxsackieviruses can use two different

receptors, coxsackie and adenovirus receptor and decay accelerating factor,^{13–15} and the receptor for FMDV is the integrin $\alpha_v\beta_3$.¹⁶ The BEV receptor has not yet been identified, but the virus can readily adapt to many varied mammalian cells in vitro (MS Smyth, unpublished data, 1990). This may imply that the receptor present on susceptible bovine cells has close homologues in these other cell lines, or that the virus can use a second receptor binding site. A second site has been shown to be used by CAV9 because the RGD motif is lost when the VP1 C-terminal extension is removed by trypsin, yet the virus retains infectivity.¹⁷ Hence, the issue of receptor binding is a complex one, even in these apparently simple viruses.

UNCOATING EVENTS

The second phase, uncoating, remains even more poorly understood. The viral capsid must be stable enough for the

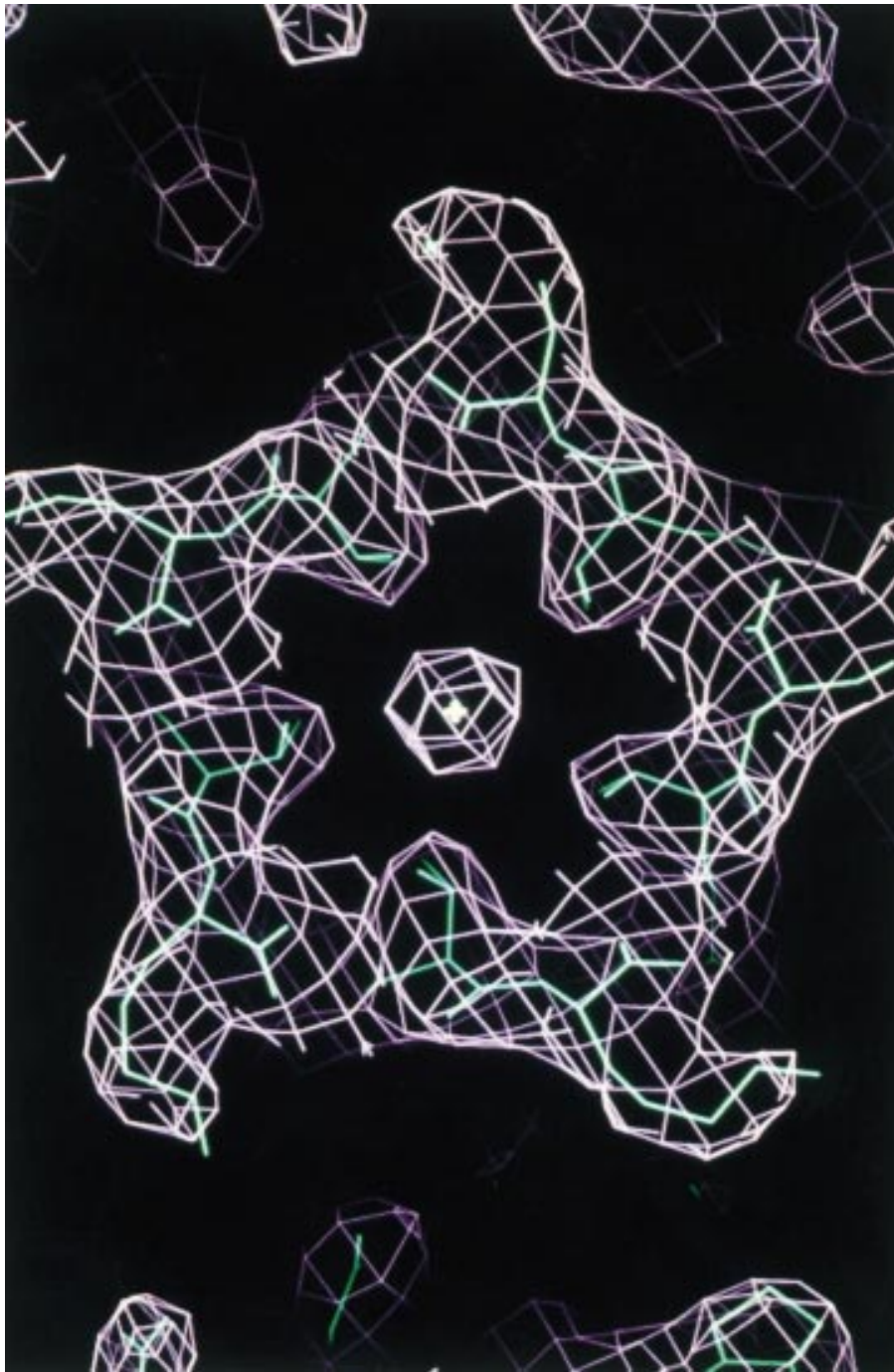


Figure 2 Electron density within the fivefold channel of bovine enterovirus (BEV). A discrete node of non-protein density consistent with a metal ion can be seen blocking the channel at this point.

virus to be transmitted between hosts while protecting the fragile RNA genome but must, at the appropriate signal, dissociate or alter in conformation sufficiently to allow genome release.

None of the electron density maps from the various picornavirus crystallographic data show an ordered structure for the genome, except for perhaps at most one or two bases stacked beneath tryptophan residues on the inner surface of the capsid.^{13 18–20} However, this is not necessarily evidence that there is true randomness in the packaging of the genome: if each virus particle in a crystal had its RNA molecule packaged in an identical conformation to the others, then because of the capsid symmetry there would be 12 possible orientations for those RNA molecules, thus giving apparent overall disorder. Even a crude calculation shows the genome packing density to be in the region of 1000 mg/ml. It seems unlikely that any

biological system could efficiently achieve this with no ordered structure.

“ The myristate covalently linked to the VP4 N-terminus, which lies close to the inner opening of the fivefold channel, may interact with the host cell membrane, causing VP4 and the genome to leave the capsid through the channel”

It has been known for some time that the loss of VP4 is an early step in the uncoating process.^{21 22} Uncoating studies with poliovirus and HeLa cell membranes showed that the loss of VP4 was accompanied by a 10–20% reduction in S value, loss of infectivity, retention of a functional genome in an RNase resistant state, and sensitivity to proteolytic enzymes and detergents.^{23 24} The genome then appears to be injected into the

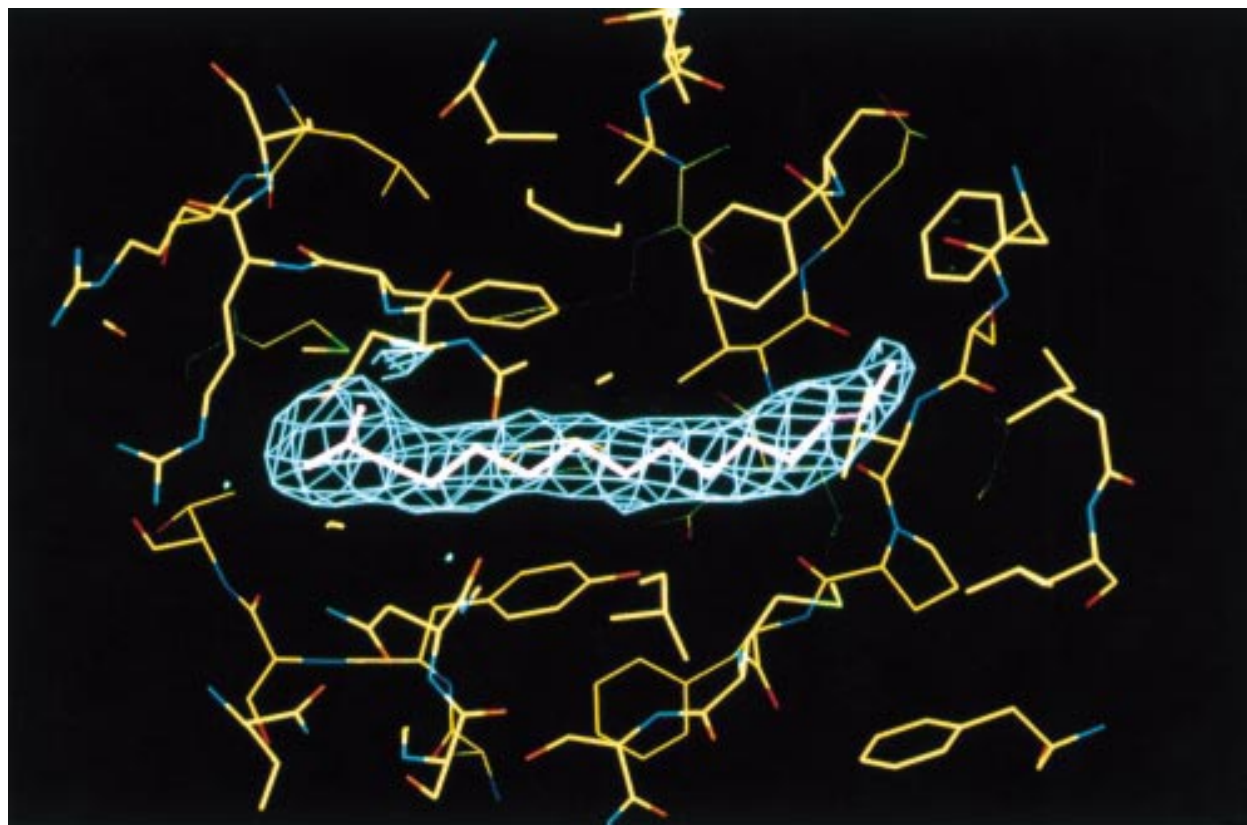


Figure 3 The hydrophobic pocket within VP1 of the bovine enterovirus (BEV) crystal structure contains electron density (blue) which has been modelled as myristic acid (white).

cytoplasm from acidic endosomes in which the virus is internalised.^{25–26} Agents such as chloroquine, monensin, tributyltin, or metabolic inhibitors that raise endosomal pH, dissipate proton gradients, inhibit acidification, or deplete ATP inhibit entry of the genome into the cytoplasm. However, because VP4 is known to be completely internal and when isolated is completely unreactive with susceptible cells, the mechanism of its release is unclear. One possibility is that the myristate covalently linked to the VP4 N-terminus, and which lies close to the inner opening of the fivefold channel, somehow interacts with the host cell membrane, causing VP4 and the genome to leave the capsid through the channel.²⁷ For this to occur, the capsid must first be destabilised because the diameter of the channel is insufficient to allow either the myristate–VP4 complex to leave or for some component of the membrane to enter. Information that also pre-dates any of the virus crystal structures is that the capsid undergoes a dramatic antigenic alteration just before uncoating.²⁸ Loss of VP4 can be induced by acid conditions or, in the case of HRV16, by treatment of the virus with a preparation of its receptor. Associated with this loss of VP4 is the transition of the N-terminus of VP1 from its position on the interior of the capsid surrounding the bottom of the channel at the fivefold axis to an external location via the channel. It has been shown that mutations in VP1 of poliovirus can inhibit uncoating; the removal of residues 8 and 9 affects only RNA release, whereas removal of residues 1 to 4 also affects encapsidation.²⁹ Virus particles that have lost VP4 have a buoyant density of 135S; they are termed A particles and are non-infectious. These A particles also have the N-terminus of VP1 externalised.³⁰ Normal infectious particles sediment at 160S.

THE FIVEFOLD AXIS CHANNEL

A channel exists at each of the fivefold axes that connects the outer surface of the capsid with the inner surface. The shape

and dimensions of the channels of the picornaviruses are very similar. Furthermore, there is frequently a metal ion binding site in the channel. In the rhinoviruses, coxsackieviruses, and ϕ X174 this is close to the outer surface, although in BEV it is deep in the channel and in CAV9 there are apparently five ions in the channel.

In BEV, the channel is a β cylinder approximately 1 nm in diameter, which is plugged at two places: by five symmetry related tyrosine side chains and beneath this by a metal ion (fig 2). This results in BEV having a lower caesium chloride buoyant density than its nearest phylogenetic neighbours.³¹ An analogous channel exists at the fivefold axes of apparently diverse viruses, such as DNA bacteriophage ϕ X174,³² the RNA nodaviruses,³³ and tetraviruses.³⁴

The proposal that this channel is where the RNA exits from the capsid is consistent with the known exit mechanism of the DNA from phage ϕ X174, where even the structure of the channel is similar.³² It has also been proposed that the channel is used for the exit of the RNA genomes of the tetraviruses³⁴ and the nodaviruses.³³

The N-terminal region of VP1, which becomes exposed just before uncoating, is located at the inner surface of the channel, but is not visible in most of the crystal structures. However, in the case of CAV9, the crystal structure of which was determined in complex with the antiviral compound WIN 51711,⁷ these residues are visible and their position is consistent with the hypothesis that the VP1 N-terminus exits via the channel. These residues are in an extended conformation in CAV9; however, in HRV16 they adopt a helix structure.²⁰ In addition, five symmetry related helices exist in an analogous position in the tetraviruses.

The five symmetry related N-termini of VP3 are also located near the inner opening of the channel. It is possible that the myristoyl moieties of VP4 may stabilise the VP3 β barrel, which is known to be essential for assembly of some picornavirus capsids.³⁰

Therefore it has been proposed that the first event in uncoating is the interaction of the myristoyl groups of VP4, through the channel, with the host cell membrane. This event would lead to the loss of VP4 (which is consistent with biochemical data), followed by the exposure, again through the channel, of the VP1 N-terminus. Together, these events somehow prepare the channel to serve as a port of exit for the RNA. To gain further insight into these mechanisms, many studies have been carried out using inhibitors of uncoating.

THE POCKET FACTOR

All of the polioviruses,^{18 35 36} coxsackieviruses,^{7 13} BEVs,³ and rhinoviruses^{2 37 38} whose structures have been solved have a hydrophobic pocket contained completely within VP1, and which is accessible through a pore on the virus surface. Many of the structures show that the pocket is occupied by a natural fatty acid "pocket factor". This is thought to be obtained upon release of the virus from the previous host cell. Studies involving the incubation of viruses with an excess of pocket factor molecules have shown that their presence has an inhibitory but reversible effect on uncoating, suggesting that a dynamic equilibrium exists between full and empty pocket states. Ismail-Cassim *et al* showed that the uncoating of BEVs was inhibited by a range of saturated fatty acids varying in chain length in the range C12 to C15, whereas the attachment to cells was unaffected.³⁹ These fatty acids have no effect on the uncoating of poliovirus or rhinovirus. Synthetic antiviral compounds, such as WIN 51711,⁴⁰ which act by the inhibition of uncoating have been shown to bind tightly within this pocket, after displacement of the natural pocket factor. Taken together, these observations suggest that the pocket factor mediates the stability of the capsid and its release is a necessary prerequisite to uncoating.

In several enterovirus and rhinovirus crystal structures solved to date, the pocket within VP1 contains a node of electron density apparently commensurate with a fatty acid. These molecules are held in place by hydrogen bonds from their carboxyl oxygens to VP1 residues, which in the case of BEV are an arginine side chain and a main chain nitrogen.³ At the same end of the pocket as this head group is the pocket pore, which is constricted in the case of BEV with three bulky side chains: arginine, phenylalanine, and tyrosine. The closed end of the pocket is lined by hydrophobic residues. In BEV the pocket factor was modelled as myristic acid (fig 3). This refined well against the *x* ray crystallographic data, suggesting a high occupancy of all 60 pockets in the virion. It also agrees with the observation that the uncoating of BEV can be reversibly inhibited in the presence of a range of excess fatty acids. However, in BEV the electron density appears to fade rather than end discretely at the aliphatic end of the molecule. This suggests either that the aliphatic end of the fatty acid is less well ordered than the hydrogen bonded carboxyl end, or that the pockets are occupied by a range of fatty acids differing in length as above.

"The pocket factor mediates the stability of the capsid and its release is a necessary prerequisite to uncoating"

A range of antiviral compounds known as the Winthrop (WIN) compounds⁴¹ have been shown to inhibit the attachment of some picornaviruses to their cellular receptors. Structural studies have shown that the WIN compounds occupy the VP1 pocket, displacing and binding more tightly than the natural pocket factor. The crystallographic technique often used for such studies involves soaking a crystal of the virus in a solution of the antiviral compound. The fact that this technique is possible is further evidence for the dynamic equilibrium theory. In addition, it is often observed that the virus crystal disintegrates during the soaking process. This

Take home messages

- Picornaviruses are small, icosahedral, non-enveloped viruses with a single positive strand RNA genome
- The structure of all picornaviruses is similar, being composed of 60 copies each of four viral proteins, VP1–4, with a channel at each of the fivefold axes, which connects the inner and outer surfaces and has a myristoyl group close to the inner opening
- The different picornaviruses attach to specific receptors on the host cell membrane by various methods
- It is thought that the first event in uncoating is the interaction of the myristoyl groups of VP4, through the channel, with the host cell membrane, which leads to the loss of VP4, and is followed by the exposure, again through the channel, of the VP1 N-terminus
- Together, these events somehow prepare the channel to serve as a port of exit for the RNA
- The genome then appears to be injected into the cytoplasm from the acidic endosomes in which the virus is internalised
- The polioviruses, coxsackieviruses, bovine enteroviruses, and rhinoviruses all contain a hydrophobic pocket in VP1 that is occupied by a natural fatty acid "pocket factor", which is thought to mediate the stability of the capsid and which is released before uncoating
- No pocket is present in the aphthoviruses, which may use a different method for uncoating

indicates that the entry of the antiviral compound into the pocket brings about structural changes that are manifested on the capsid surface, and which are sufficient to disrupt the fragile virion–virion interactions responsible for the crystal lattice.

How does the occupation of the pocket affect events at the fivefold channel? Evidence from structural studies of rhinovirus in which the pockets are occupied with antiviral compounds indicate that various conformational changes occur in the vicinity of the channel in the presence of the antivirals.²⁰ Residues at the N-terminus of VP3 that surround the interior of the channel become more rigid. Furthermore, the ion binding site in the channel becomes more occupied and the residues that coordinate with the ion also become more rigid. Evidence from the structure of CAV9 in the presence of an antiviral compound suggests that the VP1 N-terminus also becomes more ordered under these conditions. These observations are consistent with the necessity of flexibility for successful uncoating to take place. Additional evidence that the channel is the route of departure of the RNA comes from the acid treatment of HRV14, which induces uncoating: under these conditions, residues surrounding the ion binding site become more disordered.

OTHER PICORNAVIRUSES: OTHER MECHANISMS

Members of the aphthovirus genus, which includes the much studied FMDVs, have similar overall capsid architecture to the other picornavirus family members; however, important differences exist. The capsid shell has a smoother outer surface, lacking canyons or deep depressions, and there is no hydrophobic pocket within VP1.⁴ In addition, the channel at the icosahedral fivefold axis of FMDV is less constricted than that found in the rhinoviruses or enteroviruses, and is large enough in diameter to admit caesium ions, which accounts for FMDV having the highest buoyant density among all picornaviruses.⁴² The particles are highly acid labile, displaying a high concentration of histidine residues at the pentamer interfaces: the pK value of this residue being consistent with the pH of capsid dissociation. It is possible that, following internalisation, these viruses make sole use of pH dependent separation of the pentamers for uncoating.⁴³ Indeed, it has been shown that the removal of calcium ions from the

morphologically similar tomato bushy stunt virus has the same effect.⁴⁴ This being the case, it is possible that structures such as the fivefold channel and the myristoyl moieties at the N-termini of VP4 are redundant, evidence that the aphthoviruses evolved from an ancestor common to the rhinoviruses and enteroviruses.

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REFERENCES

- Putnak JR, Philips BA. Picornaviral structure and assembly. *Microbiol Rev* 1981;**45**:287-315.
- Rossmann MG, Arnold E, Erickson JW, et al. Structure of a human common cold virus and functional relationship to other picornaviruses. *Nature* 1985;**317**:145-53.
- Smyth M, Tate J, Hoey E, et al. Implications for viral uncoating from the structure of bovine enterovirus. *Nat Struct Biol* 1985;**2**:224-31.
- Acharya R, Fry E, Stuart D, et al. The three dimensional structure of foot-and-mouth disease virus at 2.9Å resolution. *Nature* 1989;**337**:709-16.
- Luo M, Viend G, Kamer G, et al. The atomic structure of Mengo virus at of 3.0Å resolution. *Science* 1987;**235**:182-91.
- Hogle JM, Chow M, Filman DJ. Three dimensional structure of poliovirus at of 2.9Å resolution. *Science* 1985;**229**:1358-65.
- Hendry E, Hatanaka H, Fry E, et al. The crystal structure of coxsackievirus A9: implications for receptor binding and enterovirus classification. *Structure* 1999;**7**:1527-38.
- Chow M, Newman JFE, Filman D, et al. Myristylation of picornavirus capsid protein VP4 and its structural significance. *Nature* 1987;**327**:482-6.
- Rowlands DJ. Rhinoviruses and cells: molecular aspects. *Am J Respir Crit Care Med* 1995;**152**:531-5.
- Chang, KH, Auvinen P, Hyypia T, et al. The nucleotide sequence of coxsackievirus A9: implications for receptor binding and enterovirus classification. *J Gen Virol* 1989;**70**:3269-80.
- Fox G, Parry N, Barnett P, et al. The cell attachment site on foot-and-mouth disease virus includes the amino acid sequence RGD (arginine-glycine-aspartic acid). *J Gen Virol* 1989;**70**:625-37.
- Olson NH, Kolatkar PR, Oliveira MA, et al. Structure of a human rhinovirus complexed with its receptor molecule. *Proc Natl Acad Sci U S A* 1993;**90**:507-11
- Muckelbauer JK, Kremer M, Minor I, et al. The structure of coxsackievirus B3 at 3.5Å resolution. *Structure* 1995;**3**:653-67.
- Bergelson JM, Mohanty JG, Crowell RL, et al. Coxsackievirus B3 adapted to growth in RD cells bind to decay-accelerating factor [CD55]. *J Virol* 1995;**69**:1903-6.
- Bergelson JM, Cunningham JA, Droguett G, et al. Isolation of a common receptor for coxsackie B viruses and adenoviruses 2 and 5. *Science* 1997;**275**:1320-3.
- Neff S, Sa-Carvalho D, Rieder E, et al. Foot-and-mouth disease virus virulent for cattle utilises the integrin $\alpha_5\beta_3$ as its receptor. *J Virol* 1998;**72**:3587-94.
- Roivainen M, Hyypia T, Piirainen L, et al. RGD-dependent entry of coxsackievirus A9 into host cells and its bypass after cleavage of VP1 protein by intestinal protease. *J Virol* 1991;**65**:4735-40.
- Filman DJ, Syed R, Chow M, et al. Structural factors that control conformational transitions and serotype specificity in type 3 poliovirus. *EMBO J* 1989;**8**:1567-79.
- Arnold E, Rossmann MG. Analysis of the structure of a common cold virus, human rhinovirus 14, refined at a resolution of 3.0Å. *J Mol Biol* 1990;**211**:763-801.
- Hadfield AT, Lee W, Zhao R, et al. The refined structure of human rhinovirus 16 at 2.15Å resolution: implications for the viral life cycle. *Structure* 1997;**5**:427-41.
- Crowell RL, Philipson L. Specific alterations of coxsackievirus B3 eluted from HeLa cells. *J Virol* 1971;**8**:509-14.
- Lonberg-Holm K, Korant BD. Early interaction of rhinoviruses with host cells. *J Virol* 1972;**9**:29-40.
- Desena J, Mandel B. Studies on the in vitro uncoating of poliovirus. Characterisation of the modifying factor and the modifying reaction. *Virology* 1976;**70**:470-83.
- DeSena J, Mandel B. Studies on the in vitro uncoating of poliovirus. Characterisation of the membrane-modified particle. *Virology* 1977;**78**:554-66.
- Madhus IH, Olsnes S, Sandvig K. Mechanism of entry into the cytosol of poliovirus type 1: requirement for low pH. *J Cell Biol* 1984;**98**:1194-200.
- Zeichardt H, Wetz K, Willingmann P, et al. Entry of poliovirus type 1 and Maus Elberfeld (ME) virus into HEp2 cells: receptor mediated endocytosis and endosomal or lysosomal uncoating. *J Gen Virol* 1985;**66**:483-92.
- Giranda VL, Heinz BA, Oliveira MA, et al. Acid-induced structural changes in human rhinovirus 14: possible role in uncoating. *Proc Natl Acad Sci U S A* 1992;**89**:10213-17.
- Fenwick ML, Wall MJ. Factors determining the site of synthesis of poliovirus proteins: the early attachment of virus particles to endoplasmic membranes. *J Cell Sci* 1973;**13**:403-13.
- Kirkegaard K. Mutations in VP1 of poliovirus specifically affect both encapsidation and release of viral RNA. *J Virol* 1990;**64**:195-206.
- Fricks CE, Hogle JM. Cell-induced conformational change in poliovirus: externalization of the amino terminus of VP1 is responsible for liposome binding. *J Virol* 1990;**64**:1934-45.
- Martin SJ, Johnson MD, Clements JB. Purification and characterization of bovine enterovirus. *J Gen Virol* 1970;**7**:103-13.
- McKenna R, Xia D, Willingmann P, et al. Atomic structure of single-stranded DNA bacteriophage ϕ X174 and its functional implications. *Nature* 1992;**355**:137-43
- Cheng RH, Reddy VS, Olson NH, et al. Functional implications of quasi-equivalence in a T=3 icosahedral animal virus established by cryo-electron microscopy and X-ray crystallography. *Structure* 1994;**2**:271-82.
- Munshi S, Liljas L, Cavarelli J, et al. The 2.8Å structure of a T=4 animal virus and its implications for membrane translocation of RNA. *J Mol Biol* 1996;**261**:1-10.
- Flore O, Fricks CE, Filman DJ, et al. Conformational changes in poliovirus assembly and cell entry. *Semin Virol* 1990;**1**:429-38.
- Yeates TO, Jacobson DH, Martin A, et al. Three-dimensional structure of a mouse-adapted type 2/type 1 poliovirus chimera. *EMBO J* 1991;**10**:2331-41.
- Kim KH, Willingmann P, Gong ZX, et al. A comparison of the anti-rhinoviral drug binding pocket in HRV14 and HRV1A. *J Mol Biol* 1993;**230**:206-25.
- Oliveira MA, Zhao R, Lee WM, et al. The structure of human rhinovirus 16. *Structure* 1993;**1**:51-68.
- Ismail-Cassim N, Chezzi C, Newman JFE. Inhibition of the uncoating of bovine enterovirus by short chain fatty acids. *J Gen Virol* 1990;**71**:2283-9.
- Smith TJ, Kremer MJ, Luo M, et al. The site of attachment in human rhinovirus 14 for anti-viral agents that inhibit uncoating. *Science* 1986;**233**:1286-93.
- Diana GD, Otto MJ, McKinlay MA. Inhibitors of picornavirus uncoating as antiviral agents. *Pharmacol Ther* 1985;**29**:287-97.
- Newman JFE, Rowlands DJ, Brown F. A physico-chemical sub-grouping of the mammalian picornaviruses. *J Gen Virol* 1973;**18**:171-80.
- Curry S, Abrams CC, Fry E, et al. Viral RNA modulates the acid sensitivity of foot-and-mouth disease virus capsid. *J Virol* 1990;**71**:430-8.
- Robinson IK, Harrison SC. Structure of the expanded state of tomato bushy stunt virus. *Nature* 1982;**297**:563-8.



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