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ICAM-1 receptors and cold viruses

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Abstract

Human rhinoviruses (HRVs), the single most important etiologic agent of common colds, are small viruses composed of an icosahedral protein shell that encapsidates a single, positive RNA strand. Multiplication of HRVs occurs in the cytoplasm of the host cell. To produce infection, HRVs must first attach to specific cellular receptors embedded in the plasma membrane. Ninety percent of HRVs immunogenic variants use as receptor intercellular adhesion molecule-1 (ICAM-1), a cell surface glycoprotein that promotes intercellular signaling in processes derived from inflammation response. As HRV receptor, ICAM-1 positions the virus to within striking distance of the membrane, and then triggers a conformational change in the virus that ultimately results in delivery of the viral RNA genome into the cytoplasm, across a lipid bilayer. The interaction between ICAM-1 and HRVs has been analyzed by the combination of crystal structures of HRVs and ICAM-1 fragments with electron microscopy reconstructions of the complexes. The resulting molecular models are useful to address questions about receptor recognition, binding specificity, and mechanisms by which ICAM-1 induces virus uncoating.

Keywords: Rhinovirus; ICAM-1; Virus–receptor; Electron microscopy

More than 200 different viruses are known to cause common colds, infections usually mild in nature that exhibit such symptoms as sneezing, nasal congestion, and decreased energy level. Human rhinoviruses (HRVs), are the most important etiologic agents for common colds (Rueckert, 1996), accounting for 30% to 50% of all adult colds and 10% to 25% of colds in children. Other cold-producing viruses are coronaviruses, adenoviruses, coxsackieviruses, echoviruses, orthomyxoviruses, paramyxoviruses, respiratory syncytial virus, and enteroviruses. Each type of virus produces infections with slightly different patterns of symptoms and severity, and some are also responsible for other, more severe illnesses.

Rhinoviruses belong to the *picornaviridae* family: small icosahedral viruses with an average diameter of 300 Å and a molecular mass of approximately 8.5×10^6 Da. Like all picornaviruses, HRVs are made of a protein capsid that encases a single-stranded, positive-sense RNA molecule of about 7000 bases. The capsid is built from 60 copies of viral proteins 1, 2, 3 and 4 (VP1, VP2, VP3, and VP4). VP1, VP2 and VP3 assemble on the exterior to form the protein shell, and VP4 resides in the interior of the capsid, in contact with the viral RNA. About a hundred different HRV serotypes have been identified, each characterized by its own specific antigens.

Three-dimensional structures of several HRV capsids have been determined to atomic detail by using X-ray crystallography (Rossmann et al., 1985; Kim et al., 1989; Oliveira et al., 1993; Zhao et al., 1996). These structures show the precise arrangement of the different viral proteins in the capsid. In all of them, a 20-Å deep depression, or ''canyon'', encircles each five-fold vertex.

1. Rhinovirus receptors and the canyon hypothesis

Most viruses initiate infection of susceptible cells by first attaching to specific cell surface receptors. Receptors have been identified for many animal, insect, and bacterial viruses, and only plant viruses seem to pose an exception. In animal viruses, the receptor determines, in part, host range and tissue tropism. Viruses are able to subvert a wide variety of cell-surface molecules as receptors. Some viruses are able to recognize very specific proteins, whereas others use sugar moieties or common chemical groups for attachment. Many viral receptors act simply as molecular tethers that concentrate virus particles on the cell surface

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and direct them towards disassembly pathways. For some viruses, however, the cell receptor plays an active role in the uncoating of the viral genome, that is the translocation of the RNA from the interior of the capsid to the host cell cytoplasm.

Not all the 102 characterized rhinovirus serotypes share the same receptor. Ninety percent, the major group, utilize the cell surface glycoprotein intercellular adhesion molecule-1 (ICAM-1) as receptor (Greve et al., 1989; Staunton et al., 1989). A minor group of about 10 HRV serotypes uses members of the low-density lipoprotein receptor (LDLR) family for cell binding (Hofer et al., 1994; Marlovits et al., 1998), and one individual serotype, HRV87, binds to a still uncharacterized receptor (Uncapher et al., 1991). ICAM-1 is also shared as receptor by several members of the Coxsackievirus-A family, another group of picornaviruses causing upper respiratory infections (Colonno et al., 1986; Shafren et al., 1997).

Amino acid residues at the bottom of the canyon are more conserved among HRVs than those that are exposed elsewhere on the viral surface (Rossmann and Palmenberg, 1988; Chapman, 1993). Hypervariable surface residues coincide with the binding sites of neutralizing monoclonal antibodies, and mutations at these sites allow the virus to escape the neutralization effect. On the basis of these residue conservation patterns, the canyon was proposed as the receptor binding site (Rossmann et al., 1985; Rossmann, 1989). It was also suggested that HRVs could hide their receptor binding site inside canyons or depressions, inaccessible to bulkier antibodies, while mutating the external residues outside the canyon to elude the host's immune surveillance. These postulates form the basis of what became known as the canyon hypothesis (Rossmann, 1989). Confirmation of the canyon as receptor binding site was provided by mutational analysis of specific residues in the canyon (Colonno et al., 1988), and by the cryo-electron microscopy (cryo-EM) reconstruction of a complex of HRV16 with a two-domain fragment of ICAM-1 (Olson et al., 1993).

2. Intercellular adhesion molecule-1

ICAM-1 is a transmembrane glycoprotein with an extracellular part composed of several immunoglobulin (Ig) domains arranged end-to-end. Ig domains are characteristic building blocks of antibodies. The structure of an Ig domain can be described as two antiparallel β-sheets packed tightly against each other, connected through several loops following a well-defined topology, and linked by one or two disulfide bridges (Harpaz and Chothia, 1994). ICAM-1 has five Ig domains (Fig. 1), a transmembrane region, and a short cytoplasmic domain. Other members of the ICAM family are ICAM-2, ICAM-3, ICAM-4 and ICAM-5. All ICAMs show the same domain organization, sequence homology between domains, and are functionally and structurally related. ICAMs differ in the number of Ig domains, cell type, and expression regulation.

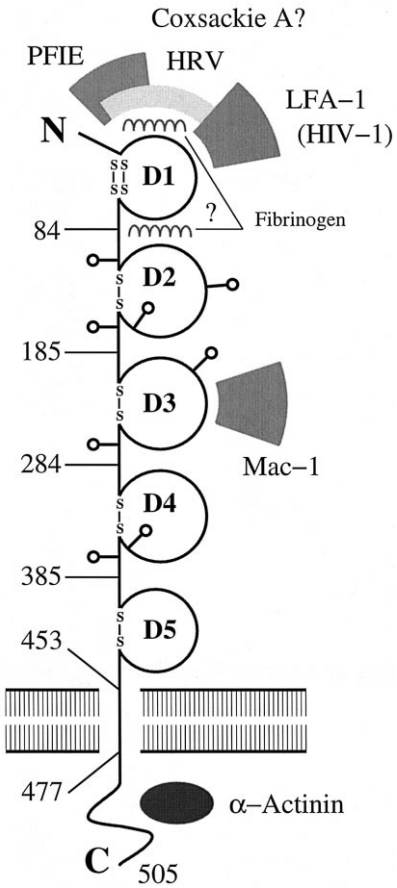

Fig. 1. Domain structure of ICAM-1. Each Ig domain is represented schematically by a circle closed by one or two disulfide bonds. Amino acid numbers indicate the beginning and end of each domain. Approximate locations of relevant binding sites are shown. Lollipop-shaped structures indicate N-linked glycosylation sites.

ICAM-1 promotes intercellular signaling, mainly in processes derived from response to inflammation. It permits antigen-independent adhesion between lymphocytes and their targets, and has a major role in leukocyte transmigration from the blood to the tissues in inflammatory sites (van de Stolpe and van der Saag, 1996). Two membrane-bound integrin receptors, leukocyte function-associated antigen (LFA-1), and macrophage-1 antigen (Mac-1) are the normal ligands for ICAM-1. Binding sites for these receptors have been identified by mutagenesis techniques and competition experiments in domains D1 and D3, respectively (Fig. 1). ICAM-1 also serves as a receptor for soluble fibrinogen, its binding site still controversial, as well as for the extracellular matrix factor hyaluronan (van de Stolpe and van der Saag, 1996). These interactions probably mediate leukocyte adhesion to vascular endothelium. The cytoplasmic domain of ICAM-1 interacts with the cytoskeleton-binding protein α-actinin (Carpén et al., 1992), determining cell surface distribution of ICAM-1 and recruitment to points of interaction with other cells.

3. ICAM-1 as pathogen receptor

Rather uniquely, ICAM-1 is also subverted as receptor by human pathogens in at least three different ways. Major group rhinoviruses and A-type coxsackieviruses use ICAM-1 to release their RNA into the host cell cytoplasm. Erythrocytes infected by the malarial parasite *Plasmodium falciparum*, are able to bind ICAM-1 in the surface of endothelial cells (Berendt et al., 1992; Ockenhouse et al., 1992), and use this cytoadherence to sequester themselves in deep vascular beds, including the brain, minimizing exposure of the parasite to immune surveillance. Finally, human immunodeficiency virus-1 (HIV-1), uses ICAM-1 as a coreceptor (Bastiani et al., 1997; Fortin et al., 1997; Rizzuto and Sodroski, 1997). HIV-1 acquires several host cell membrane proteins when it buds from infected cells, making it possible for ICAM-1 to be incorporated into the envelope of the virions. This results in an increase of subsequent virus–cell interactions, enhancement of virus infectivity, and extension of the host cell range.

Mutational studies have identified the binding sites for HRVs and PFIE at the tip of the first domain, the one that is the most distal from the membrane, next to the LFA-1 binding site (Staunton et al., 1990; McClelland et al., 1991; Register et al., 1991). Binding sites for HRV and PFIE overlap partially. Binding of coxsackievirus A to ICAM-1 is likely to be similar to that of HRVs, but may involve in some cases a second receptor (Shafren et al., 1997).

Many cell surface proteins use tandems of Ig domains to build their extracellular region. Together with the ICAMs, they constitute the Ig superfamily. Other members of the Ig-superfamily are subverted as receptors by HIV-1, poliovirus, coxsackievirus B, or murine encephalomyocarditis virus. Interestingly, no pathogen has been reported to bind specifically to ICAMs other than ICAM-1.

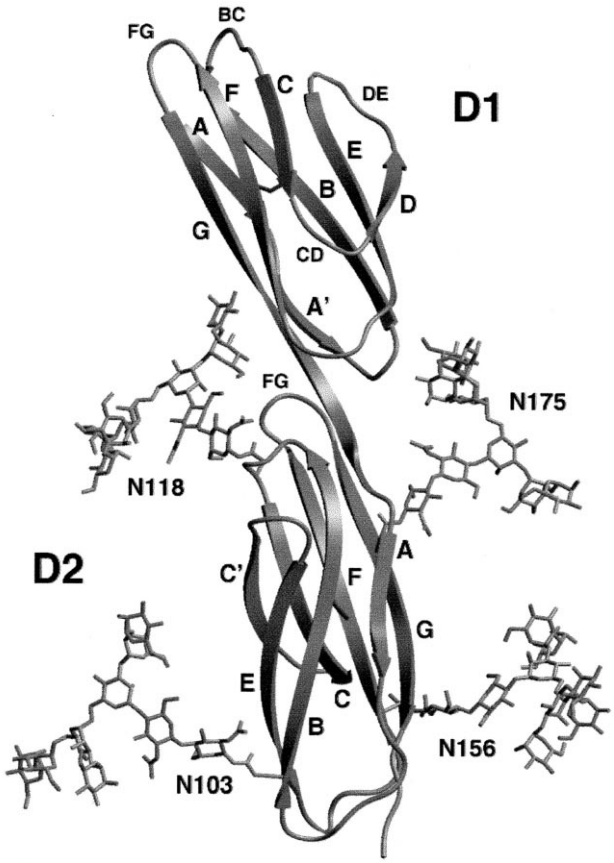

Fig. 2. Ribbon diagram of the first two domains of ICAM-1. Strands are labeled A, B, C, etc., following the convention for Ig domain nomenclature (Harpaz and Chothia, 1994). Loops are named by the strands they connect. Only functionally relevant loops mentioned in the text are labeled. Glycan models show the position of the four glycosylation sites in domain D2, linked to four asparagine residues. Only the first one or two sugars in each glycan can be identified in ICAM-1 D1D2 crystal structures (Bella et al., 1998; Casasnovas et al., 1998).

4. Three-dimensional structures of ICAM-1 fragments

Intact ICAM-1 is not amenable for structural studies. Instead, most efforts have been directed to the structural determination of soluble fragments. The structure of the two amino-terminal domains of ICAM-1 (D1D2) has been determined recently by X-ray crystallography (Bella et al., 1998; Casasnovas et al., 1998). As expected, each domain adopts an Ig fold. Binding sites on domain D1 can be mapped on the crystal structure (Fig. 2). Residues identified by mutational analysis as important for HRV binding belong to the three loops DE, BC, and FG, located at the very tip of domain D1. The interaction between ICAM-1 and LFA-1 probably requires a broad surface centered around Glu34, a residue crucial for binding located in strand C. By analogy, domain D1 could be described as a hand with three stretched fingers and a folded thumb. The tips of the three fingers (loops DE, BC, and FG) would be responsible for recognition and binding to the major group of rhinoviruses, whereas the folded thumb would be the LFA-1 recognition site. Residues important for binding ICAM-1 to malarial-infected erythrocytes map to strand B and loop CD, defining another interacting surface that differs in location from both rhinovirus and LFA-1 binding sites.

The major group of HRVs does not recognize ICAM-1 from species other than human, with the probable exception of chimpanzees, neither the homologous molecules ICAM-2 or ICAM-3. The structure of the two extracellular domains of ICAM-2 has also been determined by X-ray crystallography (Casasnovas et al., 1997). ICAM-2 D1 superimposes on ICAM-1 D1 quite well, except for significant differences in conformation located in the three loops DE, BC, and FG (Bella et al., 1998). Comparison of ICAM amino acid sequences at these loops shows major differences in the disposition of proline and charged residues, suggesting a crucial role for the three loops, the

''fingers'' of the hand, in recognition and binding between ICAM-1 and the major group of rhinoviruses.

5. ICAM-1 and the uncoating of viral RNA

Attachment of major group HRVs to ICAM-1 initiates entry in the host cell and translocation of the viral RNA across the cellular membrane (Rueckert, 1996). During this uncoating process, conformational changes take place in the viral capsid. HRVs undergo several progressive transformations when bound to cells. Infectious virions are thought to uncoat through intermediate particles characterized by the loss of VP4 and the externalization of the hydrophobic N-termini of VP1, which in turns makes the capsid hydrophobic. Intermediate particles further evolve into empty particles by release of RNA. Empty particles and most intermediate particles are noninfective, abortive products, and only a small fraction of intermediate particles attaches to the membrane and delivers the viral RNA into the cytoplasm (Rueckert, 1996).

Soluble ICAM-1 fragments have been used to reproduce in vitro some of the events described above (Greve et al., 1991; Hoover-Litty and Greve, 1993). Mixing HRVs with ICAM-1 soluble fragments produces complexes that reversibly dissociate at low temperature. Increase in temperature or receptor concentration converts these complexes into subparticles analogous to the ones seen in cell binding studies. For instance, HRV14, HRV3, and HRV16 are all converted to empty capsids when incubated with soluble ICAM-1, although the rate of uncoating depends strongly on temperature and serotype (Hoover-Litty and Greve, 1993).

6. Studying the ICAM-1/rhinovirus interaction by a combination of cryo-EM and X-ray crystallography

Reversible complexes between HRVs and soluble fragments of ICAM-1 make possible the study of their interaction by structural techniques. No atomic resolution structure of a complex between virus and receptor is available yet, but low-resolution EM reconstructions of complexes of D1D2 fragments of ICAM-1 with HRV14 or HRV16 demonstrate that, indeed, the two-domain ICAM-1 fragment binds into the central part of the canyon (Fig. 3). ICAM-1 fragments have an approximate dumbbell shape in these reconstructions, and are oriented roughly perpendicular to the viral surface, extending to a radius of about 205 Å. Three-dimensional structures for HRV14, HRV16, and ICAM-1 D1D2 are available, and they can be combined to fit molecular models into the EM reconstructions (Kolatkar et al., 1999).

Given the elongated shape of the ICAM-1 D1D2 model, ambiguity exists in its correct orientation around the major D1D2 axis. That problem can be solved by comparing EM

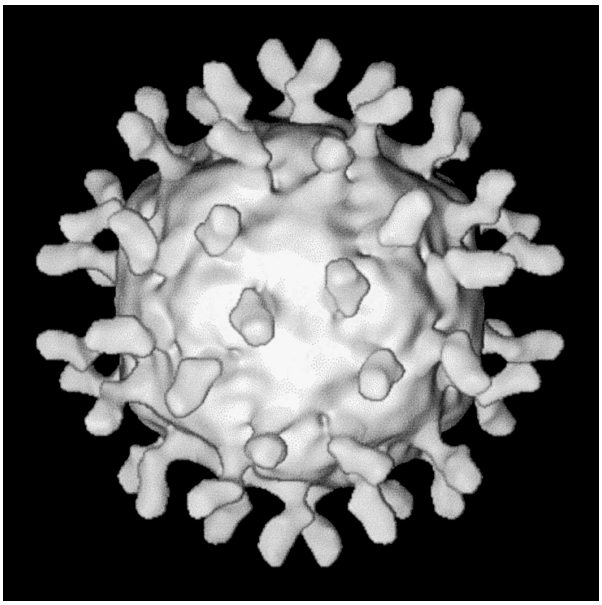

Fig. 3. Cryo-EM reconstruction of a complex between HRV16 and a low-glycosylation form of ICAM-1 D1D2 (Bella et al., 1998). There are 60 copies of the receptor fragment, visible as radial projections on the viral surface.

reconstructions from complexes of HRV16 with ICAM-1 D1D2 fragments with different degrees of glycosylation. The second domain of ICAM-1 has four N-linked carbohydrates (Fig. 1), three of which have been removed in a genetically engineered version of ICAM-1 D1D2 with reduced glycosylation (Bella et al., 1998). The reconstruction of the complex between HRV16 and this modified ICAM-1 D1D2 (Fig. 3), can be subtracted from the reconstruction between HRV16 and intact, fully glycosylated ICAM-1 D1D2 (Olson et al., 1993). The resulting difference map identifies the positions of the glycosylation sites as ''lumps'' on the surface of the density corresponding to the D2 domain, and allows to remove the orientation ambiguity (Fig. 4). Carbohydrates are intrinsically flexible molecules and can adopt a myriad of different conformations. This inherent disorder results in only the first two or three sugars from each glycosylation site being visible in crystal structures of glycoproteins, including ICAM-1 D1D2. Analogously, the lumps observed in the EM reconstructions only cover these few sugars that are closer to the protein, and therefore more ordered.

Glycosylated models of ICAM-1 D1D2 have been fit into the EM reconstructions, and the fitting refined to maximize the agreement between the density map and the atomic models (Kolatkar et al., 1999). In these models, the three loops BC, DE, and FG penetrate deep into the canyon and the short CD loop of ICAM-1 lies against VP2 of HRV14 or HRV16, on the so-called ''south'' rim of the canyon (in an analogy to the Grand Canyon and the usual representation of the rhinovirus structure, where the five-fold axis is at the top or ''north''). Analysis of the charge distribution on the interacting surfaces in both complexes

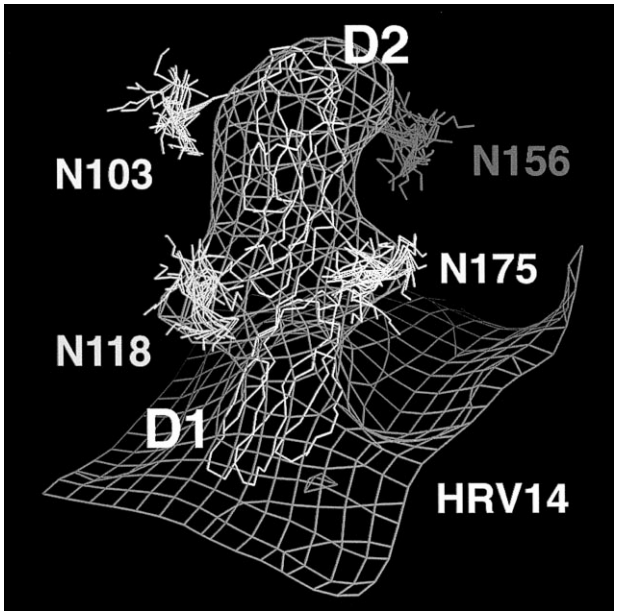

Fig. 4. Fitting of an atomic model for ICAM-1 D1D2 into the cryo-EM reconstruction of its complex with HRV14. Protein and carbohydrate are represented as C_α and C_1–C_4 tracings, respectively.

shows a remarkable complementarity. The same pattern of electrostatic interactions occurs both for HRV14 and HRV16, in spite of lack of conservation of some key residues. Thus, complementarity is not necessarily maintained as a result of residue conservation but rather by compensating changes of amino acids between serotypes.

7. Possible uncoating mechanism

The mechanisms by which ICAM-1 binding to HRV triggers virus destabilization and uncoating are not understood. A hydrophobic pocket inside VP1 lies directly beneath the canyon floor. This pocket was shown to be the binding site for certain antiviral compounds that inhibit the replication of HRVs and related picornaviruses (Fox et al., 1986; Smith et al., 1986). Experimental evidence has shown that antiviral drugs bound to this hydrophobic pocket ''lock'' the viral particle in a state in which neither VP4 nor the N-terminus of VP1 can be externalized (Lewis et al., 1998), thus preventing uncoating.

The footprint of ICAM-1 on the surface of HRV14 or HRV16 does not include the area beneath which the hydrophobic pocket is located, but it is immediately contiguous to it. Nevertheless, there is experimental evidence that the presence of antiviral compounds in the hydrophobic pocket affects cell binding for many of the major group HRVs. A two-step mechanism for the binding of ICAM-1 to HRVs can reconcile these conflicting observations. In a first step, complexes between HRVs and ICAM-1 form in a reversible manner, as they can be observed in cryo-EM reconstructions. The second step involves a displacement of the receptor attached to the virus plus a conformational change on the virus surface, resulting in a tighter, higher affinity binding between ICAM-1 and HRVs. This second step could result from conformational changes in VP1 in which the region around the hydrophobic pocket would act as a hinge (Fig. 5). Such movement would induce a destabilization in the virus capsid and perhaps the opening of a channel in the five-fold vertex through which externalization of VP4, the N-terminus of VP1, and eventually RNA could occur (Kolatkar et al., 1999). In this way, interaction between ICAM-1 and HRVs would initiate uncoating of the viral RNA.

In this hypothetical mechanism, the first step would be insensitive to the contents in the hydrophobic pocket. The presence of an antiviral compound in the pocket would impart rigidity to the hinge region and prevent the second step to occur. As a consequence uncoating would be inhibited. Conversely, empty pockets would impart conformational flexibility to the hinge region, and ultimately allow movement of polypeptide chains during the uncoating process. Crystal structures of HRVs show uncharacterized pocket molecules, probably lipidic in nature, filling the hydrophobic pocket in a manner similar to the antiviral compounds in HRV14 (Smith et al., 1986; Kim et al., 1989; Oliveira et al., 1993). It has been suggested that pocket-binding antiviral drugs displace such ''pocket factors'', and that competition between pocket factors and receptors regulates the viral stability (Rossmann, 1994). For example, ICAM-1 would be able to eject a weakly bound pocket molecule during the second step of the mechanism shown in Fig. 5, thus emptying the hydropho-

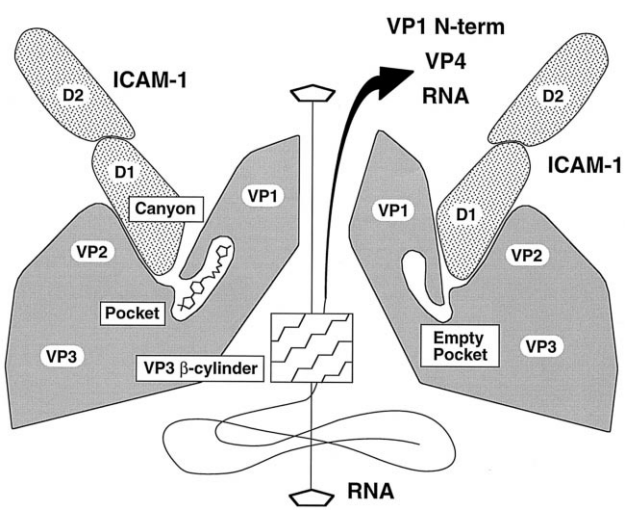

Fig. 5. Scheme of a two-step binding mechanism between ICAM-1 and major group HRVs. The first step, on the left, is observed in the cryo-EM reconstructions of HRV-ICAM-1 fragments. On the right, the second (hypothesized) step involves a conformational change in the virus surface. The five-fold channel may open as both walls and floor of the canyon bind to domain D1 of ICAM-1. The pocket region is postulated as the hinge area, and needs to be empty in order to provide conformational flexibility.

bic pocket and initiating uncoating. In contrast, a tightly bound antiviral compound would not be removed.

8. Summary

The study of the interaction between major group HRVs and their receptor, ICAM-1, suggests an hypothesis for how ICAM-1 might initiate uncoating of the viral RNA. Initial contact between the virus and receptor occurs mostly through capsid residues in the canyon and four loops at the tip of domain D1 of ICAM-1, at the end distal from the membrane. This interaction appears to have an important electrostatic component. High-affinity binding probably requires a second step in which other areas of the viral surface and the receptor may come into contact. This second step probably weakens the interactions between the capsid protomers and triggers the uncoating mechanism, perhaps through channels opened in the icosahedral five-fold axes. Capsid-binding antiviral compounds can effectively block the uncoating process by imparting rigidity to the viral capsid and preventing the high affinity binding step between ICAM-1 and HRVs. Many details need still to be addressed, and parallels sought with other picornavirus–receptor interactions. Lacking crystallographic resolution images of the virus–receptor complexes, cryo-EM reconstructions assisted with fitting of molecular models of the individual components will prove very valuable to demonstrate precisely how the virus and receptor interact, and to provide clues about the sequence of events that goes from initial cell surface attachment to release of the RNA into the host cell cytoplasm.

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