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Viral Entry Mechanisms: Diverse Strategies For Infection

Alan R. Whitmore*

Department of Virology, Northbridge Institute of Biomedical Science, Alderpoint, USA

Introduction

The initial interaction between a virus and its host cell is a pivotal and complex event that dictates the course of infection. This process, broadly termed viral entry, involves a sophisticated interplay of viral surface proteins and host cell receptors. Understanding these mechanisms is fundamental to comprehending viral pathogenesis and developing effective therapeutic strategies. This review will delve into the diverse strategies viruses employ to gain entry into host cells, highlighting the molecular details of these interactions across various viral families.

Viruses have evolved a remarkable array of molecular tools to recognize and bind to specific host cells. This specificity, known as viral tropism, is largely determined by the precise molecular interactions occurring at the host cell surface. Viral surface proteins, such as glycoproteins and capsid proteins, act as ligands that engage with complementary cellular receptors. These interactions are not static; they often involve dynamic conformational changes in both viral and host molecules, underscoring the fluidity of the entry process. Factors such as cellular conditions and receptor availability can further modulate these critical early events of infection [1].

The entry of Human Immunodeficiency Virus (HIV) provides a well-studied example of viral entry mechanisms. Key viral glycoproteins, particularly the envelope glycoproteins gp120 and gp41, play central roles in mediating HIV attachment and entry. gp120 facilitates the initial binding to the CD4 receptor on T cells, followed by interaction with co-receptors such as CCR5 or CXCR4. This binding triggers conformational changes that expose the fusion peptide of gp41, enabling membrane fusion and the release of the viral genome into the host cell. Research in this area has significantly informed the development of entry inhibitors [2].

Influenza virus, a prominent respiratory pathogen, employs a distinct entry strategy that relies on its hemagglutinin (HA) protein. HA mediates the binding of the virus to sialic acid residues present on the surface of host cells, primarily in the respiratory tract. Following cellular uptake through receptor-mediated endocytosis, the virus is enclosed within an endosome. As the endosome acidifies, HA undergoes crucial pH-dependent conformational changes that lead to membrane fusion and the release of the viral ribonucleoprotein complexes into the cytoplasm, initiating replication [3].

Coronaviruses, a group of viruses known for causing a range of illnesses from mild respiratory infections to severe diseases like COVID-19, also exhibit intricate entry mechanisms. The spike (S) protein of coronaviruses is critical for host cell recognition and entry. For many coronaviruses, including SARS-CoV-2, the S protein binds to specific cellular receptors, such as angiotensin-converting enzyme 2 (ACE2). Often, a co-receptor is also involved, facilitating the fusion of the viral envelope with the host cell membrane to deliver the viral genome [4].

Picornaviruses represent a diverse family of non-enveloped RNA viruses that utilize unique entry pathways. Unlike enveloped viruses, their entry does not involve membrane fusion. Instead, picornaviruses often bind to specific cell surface molecules, such as intercellular adhesion molecule-1 (ICAM-1) for rhinoviruses. Following receptor binding, conformational changes in the viral capsid lead to the formation of a pore or channel through the host cell membrane, allowing for the direct release of the viral genome into the cytoplasm [5].

Herpesviruses, a group of large, enveloped DNA viruses, employ a complex and multi-step entry process. Initial attachment to cellular receptors is followed by a series of events that ultimately lead to the fusion of the viral envelope with either the plasma membrane or the nuclear envelope. Viral glycoproteins are instrumental in mediating these interactions and triggering fusion. The precise mechanisms can vary among different herpesviruses, but they all culminate in the delivery of the viral genome into the host cell nucleus for replication [6].

Enveloped viruses, in general, gain entry into host cells through two main pathways: receptor-mediated endocytosis or direct fusion with the plasma membrane. Receptor-mediated endocytosis involves the engulfment of the virus by the host cell in vesicles, followed by fusion events within the endosomal compartments. Direct plasma membrane fusion occurs when the viral envelope directly merges with the host cell's outer membrane, releasing the viral contents into the cytoplasm. Both pathways are facilitated by specific viral proteins and cellular factors [7].

Paramyxoviruses, another important family of enveloped viruses, utilize specific cellular receptors, such as members of the signaling lymphocyte activation molecule (SLAM) family, for entry. Upon binding to the receptor, the viral fusion protein undergoes a conformational change that mediates the fusion of the viral envelope with the host cell membrane. This fusion event is essential for the release of the viral nucleocapsid into the cytoplasm, where viral replication can commence [9].

Host cellular factors, including microRNAs (miRNAs), can also play a significant role in regulating viral entry. miRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally. In the context of viral infection, specific cellular miRNAs can influence the expression of viral receptors or host factors that are crucial for viral entry. This represents an intrinsic host defense mechanism that can either restrict or, in some cases, facilitate viral infection [8].

Adenoviruses, a family of non-enveloped DNA viruses, are known for their efficient delivery of genetic material into the nucleus. Their entry process typically begins with binding to specific cell surface receptors, followed by endocytosis. Once inside the cell, the viral capsid undergoes destabilization within endosomes or lysosomes, leading to the release of the viral DNA, which is then transported to the nucleus for replication [10].

Description

The intricate mechanisms by which viruses gain access to host cells are central to the initiation of infection and disease. These processes are highly specific and involve a dynamic interplay between viral components and host cellular machinery. A comprehensive understanding of these entry pathways is crucial for the development of targeted antiviral therapies. This section will further elaborate on the molecular details of viral entry, drawing upon specific examples from diverse viral families.

The initial recognition and attachment phase of viral entry is mediated by specific molecular interactions between viral surface proteins and host cell receptors. These interactions are highly specific and determine the tropism of a virus, i.e., which cell types or tissues it can infect. The dynamic nature of these interactions, involving conformational changes in viral proteins and receptor availability, adds another layer of complexity to the entry process. Cellular conditions can significantly influence these dynamics, impacting the efficiency of viral entry and subsequent infection [1].

For HIV, the envelope glycoproteins gp120 and gp41 are indispensable for entry. The binding of gp120 to the CD4 receptor on T cells is the primary step, followed by interaction with a co-receptor (CCR5 or CXCR4). This sequential binding event triggers a cascade of conformational changes in gp41, exposing a fusion peptide that inserts into the host cell membrane. The subsequent refolding of gp41 drives the fusion of the viral envelope with the host cell membrane, facilitating the release of the viral capsid and genetic material into the cytoplasm. Targeting these glycoproteins and their interactions with receptors has been a successful strategy for developing antiretroviral drugs [2].

Influenza virus entry into host cells is initiated by the binding of its hemagglutinin (HA) protein to sialic acid receptors on the host cell surface. This binding event leads to the internalization of the virus through receptor-mediated endocytosis. Within the endosome, a decrease in pH triggers conformational changes in HA, promoting the fusion of the viral envelope with the endosomal membrane. This fusion event releases the viral RNA genome into the cytoplasm, where it can then proceed to the nucleus to initiate replication. Factors influencing HA-sialic acid binding specificity are key determinants of host range [3].

Coronaviruses, including SARS-CoV-2, utilize their spike (S) protein for host cell entry. The S protein binds to specific host cell receptors, such as ACE2, and often requires a co-receptor to facilitate membrane fusion. Upon binding, the S protein undergoes proteolytic cleavage and conformational changes that lead to the fusion of the viral envelope with the host cell membrane, either at the plasma membrane or within endosomes, depending on the specific virus and host cell type. This process delivers the viral RNA genome into the cytoplasm [4].

Picornaviruses employ distinct entry mechanisms due to their non-enveloped nature. They typically bind to specific cellular receptors, such as ICAM-1 for rhinoviruses. Following receptor binding, significant conformational rearrangements occur within the viral capsid. These changes lead to the formation of a pore in the host cell membrane or endosomal membrane, through which the viral RNA genome is directly injected into the cytoplasm. This mechanism bypasses the need for membrane fusion characteristic of enveloped viruses [5].

Herpesviruses exhibit a complex, multi-step entry process that often involves sequential interactions with multiple cellular receptors. Following initial attachment, viral glycoproteins mediate the fusion of the viral envelope with cellular membranes, which can occur at the plasma membrane or within intracellular compartments. In some cases, the viral capsid is transported to the nucleus, where it fuses with the nuclear envelope to deliver its DNA genome. The intricate molecular orchestration of these events is crucial for successful infection [6].

The diversity in enveloped virus entry mechanisms is remarkable. Some viruses enter via direct fusion with the plasma membrane, a process that is often triggered by specific cellular signals or pH changes. Others are internalized by the host cell through endocytosis, and subsequent fusion occurs within endosomes, which are acidified compartments within the cell. The specific pathway utilized by an enveloped virus depends on the nature of its envelope proteins and the cellular receptors it interacts with [7].

Paramyxoviruses attach to host cells via specific receptors, such as SLAM family members. The viral fusion (F) protein is instrumental in mediating membrane fusion after receptor binding. The F protein undergoes a series of conformational changes, driven by receptor interaction and potentially proteolytic cleavage, to mediate the fusion of the viral envelope with the host cell membrane. This process liberates the viral nucleocapsid into the cytoplasm [9].

The host's own molecular machinery, including microRNAs (miRNAs), can significantly influence viral entry. Cellular miRNAs can regulate the expression of genes encoding viral receptors or other host factors essential for viral entry. By modulating the availability of these targets, miRNAs can act as intrinsic antiviral defenses, restricting viral infection. Understanding these host-cell interactions opens avenues for therapeutic interventions that leverage or enhance these natural defense mechanisms [8].

Adenoviruses, non-enveloped viruses, have evolved sophisticated mechanisms to deliver their double-stranded DNA genome into the host cell nucleus. After binding to specific receptors and internalization via endocytosis, the viral capsid undergoes a series of uncoating steps within endosomes. This destabilization releases the viral DNA, which is then transported through the cytoplasm to the nucleus, a process that involves interaction with host cellular transport machinery [10].

Conclusion

Viruses employ diverse strategies to enter host cells, a critical step for infection. These mechanisms involve specific interactions between viral surface proteins and host cell receptors, dictating viral tropism. For enveloped viruses like HIV, influenza, coronaviruses, herpesviruses, and paramyxoviruses, viral glycoproteins mediate attachment and membrane fusion, either at the plasma membrane or within endosomes. Non-enveloped viruses such as picornaviruses and adenoviruses utilize different pathways, often involving capsid rearrangements and pore formation or direct genome release after endocytosis. Host factors, including microRNAs, can also modulate viral entry. Understanding these molecular mechanisms is vital for developing antiviral therapies.

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Conflict of Interest

None.

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Address for Correspondence: Alan, R. Whitmore, Department of Virology, Northbridge Institute of Biomedical Science, Alderpoint, USA, E-mail: e.morov@northbio.edu

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