

Virus-host receptor interactions in biology



Abstract

Viruses are obligate intracellular parasites and, as such, must penetrate a suitable host cell in order to replicate their genomes and disseminate. Most viruses are limited to a specific set of cells or tissues in which they can successfully replicate, and this may be in one or more particular species.

When viruses are able to bind a variety of cells, the pathogenesis and overall effect on the organism may differ. The main determinants of viral tropism differ between different virus families, but in order to take the first, and arguably most important step, in the infection of a host cell, the virus must attach via specific interactions between cell surface molecules and viral proteins. Enveloped viruses usually have proteins embedded in their envelope, assembled at the host cell surface prior to budding. In the case of some viruses (such as HIV-1), these may even consist of cellular proteins from the host cell itself. Non- enveloped viruses are usually internalized in some way and uncoated in an endosome in a pH-dependant manner.

Many viruses require a number of cell surface receptors for cell entry, and it is this combination, added to other factors such as replication proteins, that determine whether or not a virus can penetrate and replicated within a certain cell.

Introduction

As obligate intracellular parasites, the life cycle of viruses depends on an intracellular replication phase and they are thus dependant on living cells.

The first essential interaction a virus makes with a host cell is with a cell-surface receptor. A viral receptor may be defined as any cell surface

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component that mediates recognition of a cell and facilitates entry of the virus and subsequent infection. Receptors serve to ensure infection by overcoming repulsion between the virus and cell. (Baranowski, Flint, Jindrak, modern virol) Cellular receptors are generally proteins, although other types of receptor, such as carbohydrates, may be used (see table 1). These molecules are essential components of the cell or extracellular matrix and functions may include cell adhesion, signalling e. g. chemokine and growth factor receptors. (Baranowski 2003) While some viruses require only one receptor, binding to one cellular receptor alone may not be sufficient for initiation of infection for other viruses. Viruses may bind two or more receptors in sequence in order to initiate endocytosis or membrane fusion. For some viruses, the first contact with a cell is through a low-affinity interaction with a ubiquitous molecule, which allows the primary receptor-virus interaction to take place. The primary receptor is generally unique to certain cells and therefore partly defines the tropism of that particular virus, as cells are rendered susceptible to infection by a certain virus if the receptor required for attachment and entry is present. The primary attachment receptor may induce a conformational change in the viral envelope protein bound, to induce further interaction with the cell. (Modern Virology) A further interaction may then be required to initiate infection, performed by a coreceptor. The definition of the term “ coreceptor” may sometimes be ambiguous, but generally, it is taken to be the molecule that induces fusion or penetration of a cell. This may be a further determinant of tropism, for example the interaction of HIV-1...

Virus entry into a cell is the first step in the life cycle of a virus; various mechanisms of viral cell entry are shown in figure 1. The mechanism of entry varies between viruses, but all begin with the binding of a cellular receptor by a viral protein. Binding of a cellular receptor may induce endocytosis or formation of an endosome, the acidic environment of which induces uncoating; this may be dependent upon cellular proteins clathrin or caveolin. Enveloped viruses may require an acidic environment that will induce conformational changes in envelope proteins required to induce membrane fusion, while others, including the measles and HIV viruses, can fuse directly with the plasma membrane at neutral pH. (Baranowski) Fusion at the plasma membrane releases the nucleocapsid into the cytoplasm, where the virus can make its way to the nucleus or begin replication in the cytoplasm. The differences in these entry pathways are due to the nature of the molecular interactions between the viral components and target-cell receptors, for example, viruses that mimic the natural ligand of receptors for signalling molecules interfere with their signalling to promote viral entry into the cell and spread of infection. (Bomsell)

Conformational changes resulting from the binding of a primary receptor that allow the binding of a fusion receptor are a common mechanism among various types of virus, including influenza and HIV type 1, ... examples and brief description. Similar to Influenza .

Multiple receptors could be coreceptors and act together either to modulate each other or to contribute complementary functions. Alternatively, the receptors might act sequentially. Binding of the virus to the first receptor could cause changes in the virus or host that are necessary before the

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second receptor can bind (50). For those viruses in fluids with flow, such as blood or respiratory secretions, the initial binding must be able to effect rapid docking of the virus to its host cell. (Haywood)

As previously stated, some viruses recognise more than one cellular receptor. The same receptor may also be used by more than one type of virus. (see table 1) Often, these are highly abundant in many tissues, for example, heparan sulfate can serve as a receptor for many viruses, including Human immunodeficiency virus, Hepatitis C and Dengue Virus and as a co-receptor for Herpesviruses (excluding EBV). (O'Donnel) CAR, acts as a receptor for both coxsackie and adenoviruses. (Schneider) Table 1 illustrates the diversity of cell surface molecules which viruses have adapted to recognise. Some viruses use more than one type of molecule as a primary receptor e. g. reoviruses bind to the beta-adrenergic receptor as well as NAN. (Flint)

While the presence of certain receptors on host cells is vital to initiate infection, these interactions are not always sufficient to explain all aspects of cell, tissue and species tropism. (Flint)(Haywood, Schneider) Binding of a viral protein to a cell surface receptor does not necessarily mean a productive infection will follow, since a co-receptor may be absent or functional domains of the receptor may be blocked. (Baranowski) Absence of specific cytoplasmic or nuclear molecules may hinder the replication of some viruses, despite their permissivity. However, even a non-productive infection may induce pathogenic effects, for example, binding to specific receptor may induce the secretion of cytokines. (Schneider) A virus generally cannot infect a cell successfully in the absence of its specific receptor, so the distribution

around the body of the receptor will act as a restriction on the range of tissues that can be infected and hence on the number of systems in the body where signs and symptoms of infection might be experienced. (Flint)

In the true sense of the word, Tropism refers to the specific cells a particular virus is able to replicate in, although the use of receptor by a virus is increasingly a valid definition in the field of virology. Additional factors the cause viral tropism will not be considered in the context of this essay, although they may be mentioned briefly where relevant, since the focus of this review is the link between specific receptor usage and virus tropism and pathogenesis. (Kuhmann)

The primary topics explored here are the virus-receptor interactions with cells that allow viruses to enter cells and initiate infection and how this relates to the tropism of the virus at a cellular and organismal level. I am to demonstrate how viral attachment and entry is often a complicated multi-step process, sometimes requiring many different cell and virus molecules. The viruses largely used to illustrate these points, Human Immunodeficiency Virus type 1 (HIV-1), Influenza A and Herpes Simplex Virus type 1 (HSV-1) are human viruses of medical significance, but the tropism of these particular viruses in other animals, along with other viruses specific to other animals will be discussed where relevant. The structure and genomic organisation of these viruses is irrelevant and is only discussed where it relates to the glycoproteins that interact with cellular receptors. Viruses of plants, fungi and bacteria are not discussed

The presence on the cell surface of a protein that has been identified as the receptor for a given virus may not be sufficient for a productive viral infection, and there may be multiple mechanisms behind such restrictions: functional domains of the receptor may be blocked in some cellular context, additional proteins (or other cofactors) may be needed, or cells may exhibit impediments for completion of the infection cycle, despite an initial successful interaction with a functional receptor.

HSV- Demonstrates how viruses may use a large number of viral proteins and receptors to bind and enter specific cells. (Hayashi and Yoon) and how the interactions are a complex multi-step process.

Influenza - multiple steps. binds many cell types Tropism is dependent on other receptors and interactions. Of the many examples, the interaction of the human influenza A virus hemagglutinin with N-acetylneuraminic acid, and the ensuing conformational alterations involved in pH-dependent membrane fusion, are one of the best characterized at the structural and functional levels (11) (Baranowski 2001) example of proteolytic cleavage to aid spread and pathogenesis.

Conformational change required for fusion

HIV A well-documented case of use of multiple receptors is that of HIV-1 viruses and related viruses. Illustrates how a virus may use multiple coreceptors to mediate entry to different types of cells and thus influence the tropism of this virus. Uses some of the same receptors as other viruses (parallels between HIV, HSV and influenza)

Multi-step process

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The interaction of the virion with the attachment receptor leads to the first conformational changes in the envelope proteins.

This step enables the interaction with co-receptors, or entry mediators and further conformational changes at the plasma membrane.

In enveloped viruses (top), this may deliver the energy for the direct fusion of the viral envelope and cellular membrane. Some enveloped and non-enveloped viruses require the low pH in acidic endosomes to induce this conformational change. Enveloped viruses may require the low pH to induce membrane fusion (centre).

These mechanisms lead to the release and possibly uncoating of the virus genome, and the initiation of the virus replication cycle.

Role of Viral Receptor Destruction

While non-enveloped viruses typically undergo release through cytolysis. Influenza and HIV-1 Viruses also demonstrate the importance of receptor-destroying activity on the infectivity of some viruses. This is imperative for the efficient release and cell-cell spread of the virus by preventing the glycoproteins on the newly-emerged virus from binding to the host cell receptors. It is also important for preventing superinfection of cells by the same or different viruses utilising the same receptor, which may result in cell death. The efficient budding and release of Influenza A virus from the host cell relies on the removal of Sialic Acid residues by Neuraminidase. In contrast, the HIV-1 virus gp120 envelope glycoprotein downregulates the CD4 receptor after infection of monocytes, by stimulating TNF- α production. Other cellular mechanisms contribute to down-modulation of CD4, including

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the gene product Nef, which causes CD4 internalisation respectively. The precursor of gp120 and gp41, gp160, has also been found to bind CD4 intracellularly in the presence of viral protein Vpu, resulting in retention of CD4 in the Endoplasmic Rectilium.

Enveloped particles leave the infected cell inconspicuously by budding and secretion. Nonenveloped viruses are usually thought to undergo release through cell lysis, but some may escape by secretory mechanisms after budding into membrane bound compartments and then losing their membrane (Altenburg et al., 1980). Others may subvert cellular autophagy pathways to gain access to exocytic organelles (Jackson et al., 2005). (Marsh)