Virus Receptors:Implications for Pathogenesis and the Design of Antiviral Agents

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بسم ا   الرحمن الرحيم

"قال رب اشرح لى صدرى ويسر لى
امرى واحلل عقدة من لسانى يفقهوا
قولى"

صدق ا   العظيم

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ABSTRACT

The first step in virus-cell interaction is a specific binding between attachment sites on the surface of the virion and receptors on the plasma membrane of the host cell.

Virus receptors can be defined as cell surface molecules that bind the incoming viruses to the cell. They also promote entry by: inducing conformational changes in the virus that lead to priming, association with other receptors, membrane fusion and penetration, transmitting signals through the plasma membrane that lead to virus uptake or penetration and guiding bound virus particles into a variety of endocytic pathways.

The one factor that unifies all virus receptors is that they did not evolve and are not manufactured by cells to allow viruses to enter cells; but they are molecules required for normal cellular functions.

Key Word

Virus receptors , Implications for Pathogenesis

And the Design of Antiviral Agents

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CONTENTS

Introduction

A virus initiates infection by attaching to its specific receptor on the surface of a susceptible host cell. This prepares the way for the virus to enter the cell. In some cases, the receptor also plays an important role in entry in addition to its role in virus binding. Consequently, the expression of the receptor on specific cells or tissues in the whole host is a major determinant of the route of virus entry into the host, the pattern of virus spread in the host, and the resulting pathogenesis. Viral receptors are also of potential practical significance because the rational design of drugs that inhibit virus receptor interactions at the points of virus attachment or entry provides an approach to the therapeutic treatment of viral diseases **(Norkin, 1995).**

Receptor molecules may be proteins (usually glycoproteins - specific molecules), or the sugar residues present on glycoproteins or glycolipids (less specific). Two of the best studied virus-receptor interactions are Influenza virus (Hemagglutinin spikes attach to sialic acid of plasma membrane) and Human Immunodeficiency Virus (HIV I & II): Envelope contains glycoprotein spikes (gp120) which attach to CD4 receptors of T cell (**Altmeyer, 2004).**

Other identified receptors, such as the C-type lectins DC- and L-SIGN might play an important role in infection for a large number of enveloped viruses by capturing, concentrating and transmitting infectious virions **(Altmeyer, 2004).**

Viruses may either have the intrinsic capacity to use more than one receptor, as found for complex viruses such as herpes viruses **(Tufaro, 1997)** or they may compete for the same receptor; CAR (coxsackie virus–adenovirus receptor **(Bergelson *et al.*, 1997; Roelvink *et al.*, 1998).**

Receptors can be major mediators of virus tropism; after receptor interaction, both enveloped and nonenveloped viruses must deliver their genome across either the endosomal or plasma membrane for infection to proceed. Genome delivery occurs either by membrane fusion (in the case of enveloped viruses) or by pore formation or other means of permeabilizing the lipid bilayer (in the case of nonenveloped **(Sieczkarski & Whittaker, 2005).**

Viruses can be divided into two groups with respect to their interactions with receptor molecules: those with high affinity to their receptors (e.g., rhinovirus, poliovirus, and HIV) and those with low affinity (e.g., polyoma, SV40, and influenza). As a rule, the high affinity interactions serve a dual function; in addition to attachment they also induce conformational changes needed for the subsequent stages of entry. The low affinity interactions require a low pH trigger for entry **(Dimitrov, 1997).**

Indeed, the earlier view that virus receptor interactions resemble the interactions of simple ligands with their receptors, defined largely by factors such as ionic strength, pH, and temperature, has gradually given way to a view of a more dynamic multistep process. For some viruses, this means that initial binding might be followed by a secondary binding step involving other sites or components on the virus and the cell **(Haywood, 1994).**

The secondary interactions might strengthen adhesion and enable penetration either by fusion or endocytosis. Each of these steps might entail conformational changes in viral and cellular components that are necessary to promote subsequent stages of binding and entry. These complexities largely account for why much remains to be done before the details and sequences of events in virus binding and entry are completely understood **(Norkin, 1995).**

Virus entry is a very attractive target for inhibition. It is an important stage of the virus life cycle that determines to a large extent the viral tropism and pathogenesis. The participating molecules are exposed to the extracellular medium and therefore are relatively easier to reach than intracellular targets **(Dimitrov, 1997).**

In 2003, the first virus entry inhibitor, the anti-HIV peptide T20 (Fuzeon, enfuvirtide), was approved for treatment of advanced Human Immunodeficiency Virus Type 1 infection. T20 is an unconventional antiviral drug, as it does not target a viral replicase or protease but a conformational transition within the HIV1 fusion protein gp41 required for virus-cell membrane fusion **(Altmeyer, 2004).**

AIM OF THE WORK

- This review will explain virus receptor interactions, their role in pathogenesis.
- To explain recent progress in the development of therapeutics that target the level of virus entry.

Chapter 1
Viral infection

The first event in viral infection process is the binding between viral surface proteins and virus receptors or attachment factors on the surface of the host cell. This involves the specific recognition between specialized receptor-binding domains on the virion surface and receptor molecules on the cell. In many cases the specificity of this interaction is a major determinant of cell tropism and can, therefore, be an important factor in defining the pathogenesis of infection **(Rowlands, 2005).**

Until the 1980s, the understanding of attachment lagged far behind that of other steps in viral replication, because technical limitations prevented scientists from identifying viral receptors. As a result of the development of monoclonal antibody and recombinant DNA methods, this field has exploded with the identification of receptors for a number of medically important viruses, including human immunodeficiency virus type 1 and poliovirus. With the isolation of viral receptors came the ability to understand the virus-receptor interaction at a molecular level, to learn how the interaction leads to uncoating of the viral genome, to design novel antiviral therapies, and to produce new transgenic mice models for studying viral disease prevention **(Franklin, 2004).**

Once a virus has attached to a cellular receptor, it must enter the host cell so that genome expression and replication can begin. Early studies of virus entry into the host cell, from the 1950s until the late 1970s, led to the view that viruses enter by an entirely passive process: virus particles attached to the cell surface, are taken up into the cell, release their genomes, and begin to replicate. No active role for the receptor in the release of the viral genome into the cell. Beginning in the 1980s, the techniques of cellular, molecular, and structural biology were applied to elucidate the earliest events in viral infection. It is now understood that virus entry into cells is not a passive process but rather relies on viral usurpation of normal cellular processes, including endocytosis, membrane fusion, vesicular trafficking, and transport into the nucleus **(Franklin, 2004).**

Viral infection is initiated by a collision between the virus particle and the cell, a process governed by chance. Therefore, a higher concentration of virus particles increases the probability of infection. However, a virus is not able to infect every cell it encounters; it must come in contact with the cells and tissues in which it can replicate. Such cells are normally recognized by means of specific virion-cell surface receptor interaction, depending on the virus and the distribution of the cell receptor. The presence of such receptors determines whether the cell will be susceptible to the virus. However, whether a cell is permissive for the replication of a particular virus depends on other intracellular components found only in certain cell types. Cells must be both susceptible and permissive if an infection is to be successful **(Franklin, 2004).**

Virus receptors can be defined as cell surface molecules that bind the incoming viruses to the cell, and in addition, promote entry by:

- Inducing conformational changes in the virus that lead to priming, association with other receptors, membrane fusion and penetration.
- Transmitting signals through the plasma membrane that leads to virus uptake or penetration and prepare the cell for the invasion.
- Guiding bound virus particles into a variety of endocytic pathways **(Helenius, 2008).**

Attachment factors help to concentrate the virus particles on the surface of the cell, thus enhancing entry and infection. Unlike receptors, however, they do not actively promote entry and mediate signals. Often, the interactions with attachment factors are not highly specific. Indeed, the difference between receptors and attachment factors is not always simple and straight forward **(Helenius, 2008).**

Viral attachment proteins (VAP):

Many enveloped viruses display their attachment proteins as surface spikes that project perpendicularly from the viral envelope. These spikes are visible in electron micrographs and consist of oligomers of virus-specified integral membrane glycoproteins **(Figure 1)**. These glycoproteins have the bulk of their mass outside the membrane with the receptor-binding domain prominently exposed. Other domains in the same protein may be responsible for membrane fusion and receptor destruction **(Ball, 2005).** Glycoprotein–receptor interactions exist for several enveloped viruses including hemagglutinin (HA) of influenza virus with bound sialic acid **(Skehel & Wiley, 2000)**, gp120 of HIV-1 with bound CD4 and gp42 of Epstein-Barr virus with bound human lymphocyte antigen (HLA)–DR**.**

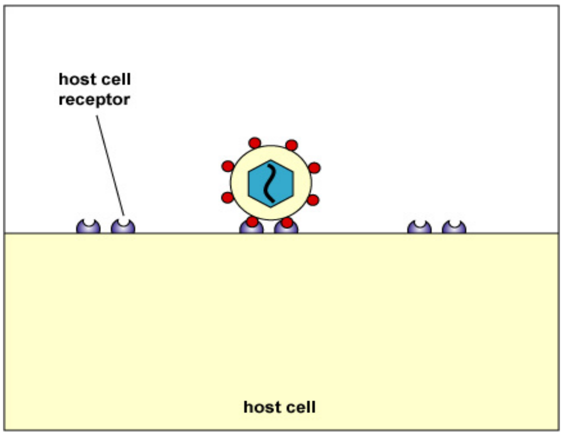

Figure (1): Adsorption of an enveloped virus to a susceptible host cell **(Kaiser & Suchman, 2007).**

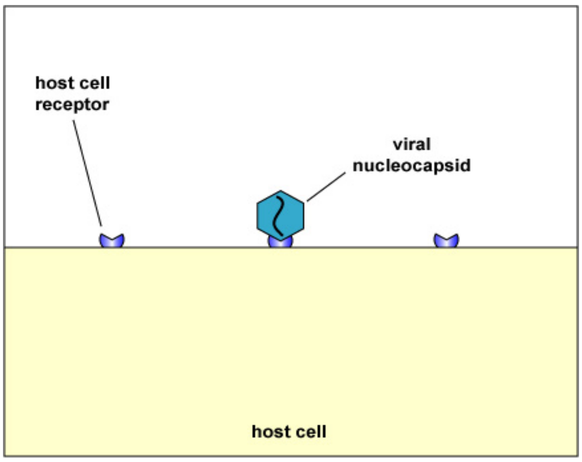

Figure (2): Adsorption of a naked virus to a susceptible host cell **(Kaiser & Suchman, 2007).**

In non enveloped viruses, the receptor-binding sites are projections or indentations in the capsid surface **(Figure 2) (Ball, 2005).** The receptor binding site can involve a single protein or a surface composed of several polypeptide chains. Adenoviruses have trimeric fiber proteins with globular knobs that project from the capsid interact with CAR (coxsackie adenovirus receptor) **(Zhang & Bergelson, 2005).** Many enterovirus receptors bind in a cleft in the capsid surface called the canyon **(Rossmann *et al.*, 2002).**

Cellular receptors for viruses:

The one factor that unifies all virus receptors is that they did not evolve and are not manufactured by cells to allow viruses to enter cells; but they are molecules required for normal cellular functions **(Cann, 2005).**

The cell receptor may determine the host range of a virus, its ability to infect a particular animal or cell culture. For example, poliovirus infects primates and cultured primate cells but not mice or mouse cell cultures. Mouse cells synthesize a protein that is homologous to the poliovirus receptor but is sufficiently different so that poliovirus cannot attach to it. In this example, the poliovirus receptor is the determinant of poliovirus host range. However, production of the virus receptor in a particular cell type does not ensure that virus replication will occur. Some primate cell cultures produce the poliovirus receptor but cannot be infected. The restricted host range of the virus in such cells is most likely due to block in viral replication beyond the attachment step **(Franklin, 2004).**

Types of cellular receptors:

Many different cell surface molecules (proteins, carbohydrates and lipids) can serve as receptors for the attachment of viruses **(Table 1).**

Carbohydrate receptors:

In some cases, a carbohydrate modification is recognized, carbohydrate groups are usually less specific receptors, because the same configuration of the side chains may occur on many different glycosylated membrane-bound molecules, so viruses that use carbohydrate receptors tend to have a broad host range **(Cann, 2005**). Glycoproteins with terminal sialic acid-bearing oligosaccharides, serve as specific receptors for a variety of viruses, including influenza A virus, sendai virus and reovirus type 3. Heparan sulfate is another example for carbohydrate receptor for many viruses, including herpes simplex virus-1 and human cytomegalovirus. Glycolipids as galactosyl ceramide which serves as a receptor for HIV-1 is also an example for carbohydrate receptors **(Young, 2001).**

Protein receptors:

On the other hand, a specific protein may be present on the surface of certain cell types acting as a receptor **(Figure 3)**. For example:

- Immunoglobulin-related proteins as (CD4 on T lymphocytes for HIV-1 and human herpes virus-7, intercellular adhesion molecule ICAM-1 for the major subgroups of rhinoviruses, coxsackie adenovirus receptor CAR for coxsackie B viruses and adenoviruses).