REVIEW

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Animal Virus Receptors

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ABSTRACT. The term 'receptor' is generally accepted as the cell-surface component that participates in virus binding and facilitates subsequent viral infection. Recent advances in technology have permitted the identification of several virus receptors, increasing our understanding of the significance of this initial virus–cell and virus–host interaction. Virus binding was previously considered to involve simple recognition and attachment to a single cell surface molecule by virus attachment proteins. The classical concept of these as single entities that participate in a lock-and-key-type process has been superseded by new data indicating that binding can be a multistep process, often involving different virus-attachment proteins and more than one host-cell receptor.

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Abbreviations:

AchR	acetylcholine receptor
ASFV	African swine fever virus
Bgp	biliary glycoprotein
BHK	baby hamster kidney
BVDV	bovine viral diarrhea virus
CAR	coxsackie and adenovirus receptor
CCR, CXCR	chemokine receptors
CD	cluster of differentiation
CDR	complementarity-determining region
CEA	carcinoembryonic antigen
CHO	chinese hamster ovary
EMC	encephalomyocarditis
DAF	decay accelerating factor
F	fusion protein
FMDV	foot-and-mouth disease virus
GaLV	gibbon ape leukemia virus
GD1	ganglioside D1
GNA	Galanthus nivalis agglutinin
HA	hemagglutinin
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HN	hemagglutinin-neuraminidase
HSV	herpes simplex virus
HPTLC	high performance thin-layer chromatography
ICAM	intercellular cell-adhesion molecule
JEV	Japanese encephalitis virus
LDLR	low-density lipoprotein receptor
LESTR	leukocyte derived seven-transmembrane domain receptor
LFA	leukocyte functional antigen
MCAT	murine cationic amino acid transporter
MHC	major histocompatibility complex
MHV	mouse hepatitis virus
MuLV	murine leukemia virus
NA	neuraminidase
PHA	phytohemagglutinin
PRCV	porcine respiratory coronavirus
PVDF	polyvinylidenedifluoride
RCA	regulator of complement activation
RGD	arginylglycylasparagine
SFV	Semliki forest virus
SIN	Sindbis virus
SIV	simian immunodeficiency virus
TBE	tick-borne encephalitis
TGEV	transmissible gastroenteritis virus
VCAM	vascular cell-adhesion molecule
VEE	Venezuelan equine encephalitis
VLA	very late antigen
WGA	wheat-germ agglutinin

1 INTRODUCTION

Despite the importance of virus receptors, the identities and host-cell functions of relatively few are presently known or widely accepted. In addition, there is only scant information available concerning the molecular mechanisms that underlie virus binding and entry. The earlier view that virus–receptor interactions

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resemble the interactions of simple ligands with their receptors has gradually given way to a view of a more dynamic multistep process. This means that initial binding might be followed by a secondary binding step involving other sites or components on the virus and the host-cell membrane. The secondary interactions might strengthen adhesion and permit penetration either by direct fusion or endocytosis. Initial binding between virus and host-cell membrane receptor is usually followed by major rearrangement of both counterparts. Cellular signaling pathways may participate in endocytotic processes required by some viruses for entry. Fusion of some viruses with a membrane changes its fluidity, permeability and other physical characteristics and may result in cell damage or even death, especially in case of enormous local viral load.

In addition to the fundamental biological and clinical importance of virus receptors, they are also of practical significance because the rational design of drugs that inhibit virus–receptor interactions at the points of virus attachment or entry provides a novel approach to the therapeutic treatment of virus diseases.

Although attempts to understand the growth of viruses in cells has occupied much of the efforts of virologists in recent years, viruses are still among the major causes of human and animal disease. The specificity of virus–receptor interactions clearly affects the species specificity of virus infection, and in some instances may be an important determinant of viral tissue tropism. An understanding of the molecular basis of host specificity, vector competence, and tissue tropism of a particular virus would be greatly facilitated by a better understanding of virus–receptor interactions.

This review emphasizes receptors for major groups of animal viruses. We provide the reader with some information about recent progress in receptor research, focusing mainly on new discoveries in this rapidly growing area.

2 GENERAL TECHNIQUES FOR RECEPTOR IDENTIFICATION

Several common approaches have been used in the past to identify viral receptors, including new progressive techniques.

The availability of recombinant DNA technology and monoclonal antibodies provided powerful approaches to identification of virus receptors. A common approach is to screen monoclonal antibodies against cell-surface antigens and determine whether any of the antibodies protect cells against viral infection. Virus overlay assays are often used to identify molecules, be it proteins or glycolipids, that are able to bind viral particles or purified viral proteins. The proteins of a cell or its membrane are separated by gel electrophoresis, transferred to a solid support (nitrocellulose or PVDF membrane) and overlaid with the virus to determine whether the virus binds to any of the separated proteins. Similarly, glycolipids are separated on a thin-layer chromatogram (HPTLC) and overlaid with virus (Karlsson and Stromberg 1987). Glycolipids also can be incorporated into liposomes and then tested for their ability to bind the virus. The receptor activity of any polypeptide or glycolipid so identified can be confirmed by the other methods available. An anti-idiotypic antibody made against a monoclonal antibody which interacts with a virus at the site of virus binding to the host cell surface may provide an internal image of the cell attachment site and provide a reagent to identify the cellular receptor. Anti-idiotypic antibodies have proven useful in the identification of cellular receptors for polyomavirus, reovirus type 3, leukemogenic retrovirus, Sindbis virus and others (Ubol and Griffin 1991; Ardman *et al.* 1985; Kauffman *et al.* 1983; Marriot *et al.* 1987; Noseworthy *et al.* 1983).

One of the most convincing methods is to transfer the gene for a potential receptor into a non permissive cell line and demonstrate that the cell acquires the ability to bind the virus and be infected by it.

Recent progress in receptor research supports our opinion that several independent approaches must lead to the same 'receptor' molecule before one can conclude, with some degree of certainty, that the molecule in question is a viral receptor. Virions are made of many identical molecules; therefore, even weak, nonspecific interactions may be strengthened by several orders of magnitude in the case of binding to a polymeric counterpart with good conformational flexibility. Moreover, many viral-surface glycoproteins are extensively glycosylated and, therefore, may be proper targets for ubiquitous lectins, which may complicate the assays used. Indeed, many 'receptors' had a rather short 'half-life'. Thus, any definitive conclusions in receptor research must be done with extra care. For instance, apparent lack of saturable binding sites on the cell may in fact not necessarily mean the lack of receptors; binding of viruses to abundant proteoglycans (heparin, heparan sulfate) explains the inability of some viruses to saturate the binding sites on cells. Indeed, saturability may appear if ionic strength of incubation media increases.

3 NATURE OF VIRUS–RECEPTOR INTERACTIONS

Members of the same virus family or even genus do not necessarily have similar receptors. Some of them recognize more than one receptor. This property appears to be common rather than exceptional. Multiple receptors could be co-receptors and act together either to modulate each other or to contribute complementary functions. Alternatively, the receptors might act sequentially. Virus binding might be analogous to adhesion of lymphocytes to endothelium, which involves rapid binding to one receptor to capture the lymphocyte followed by slower binding to a second receptor (Lawlence and Springer 1991).

Some aspects of early events in virus–host-cell interaction have been reviewed (Haywood 1994). Present data suggest that binding is followed by a cascade of interactions that include changes in the nature of the binding and in the structure of the virion, but precise details and sequence of events are not yet fully understood.

For most viruses, attachment to cell membranes *via* an interaction with cell surface proteins is the primary determinant of tropism, and many viral receptors are now well characterized. Echoviruses 1 and 8 use integrin $\alpha_2\beta_1$ (VLA-2) (Bergelson *et al.* 1992); the $\alpha_V\beta_3/\beta_5$ integrins function as secondary receptors for adenovirus (Wickham *et al.* 1993); cytomegalovirus (Price 1994) and simian virus 40 (Breau *et al.* 1992) bind to MHC I proteins. Recently, Evander *et al.* (1997) reported identification of the α_6 integrin as a candidate receptor for papillomaviruses.

Viruses with protein receptors usually have narrow host ranges and often a limited tissue tropism. A wide host range could result from using a highly conserved receptor that has domains invariant among the different organisms infected, or from using more than one protein as receptor, or both. Arthropod-borne alphaviruses and flaviviruses may serve as examples.

At least two distinct pathways evidently operate in the entry of enveloped viruses into animal cells. Some viruses penetrate the cell by direct fusion of the viral envelope with the plasma membrane. Paramyxoviruses, for example, fuse directly with the cellular plasma membrane under physiological conditions (Poste and Pasternak 1978). Other viruses fuse with plasma membranes only at a nonphysiologically, low pH level (Gonzales-Scarano *et al.* 1984; Helenius *et al.* 1980; Matlin *et al.* 1981; White *et al.* 1981). The second pathway for enveloped virus entry involves cellular uptake by endocytosis (Marsh and Helenius 1980; Marsh *et al.* 1982, 1983).

Endocytosed virions travel to membrane-bound intracellular compartments where acidic conditions are maintained (Okhuma and Poole 1978; Tycko and Maxfield 1982). The low pH of this cellular compartment apparently facilitates fusion between the viral envelope and the vesicle membrane and results in release of the nucleocapsid into the cytoplasm.

The involvement of cellular host factors other than cell-surface receptors in permissiveness to viral infection has been documented extensively. For instance, mouse cells expressing the HIV receptor CD4 are not permissive to HIV replication (Maddon *et al.* 1986; cf. Simeoni *et al.* 1998), and mouse and Chinese hamster cells expressing decay-accelerating factor CD55 are not susceptible to infection with echovirus 7 and related viruses (Ward *et al.* 1994).

Some retroviruses and most negative-stranded RNA viruses are known to incorporate cellular actin into the virion, which may account for 1–2 % of the total virion proteins. In addition, heat-shock protein 70 and actin-binding band 4.1 superfamily proteins have been shown to incorporate themselves into many negative-stranded RNA viruses (Sagara and Kawai 1992; Naito and Matsumoto 1978; Sagara *et al.* 1995). Their potential role in virus entry and/or maturation as well as their possible signaling ability remains questionable.

Several reviews concerning animal viruses have appeared during the past few years (Haywood 1994; Wimmer 1994; Norkin 1995; Weiss and Tailor 1995).

4 RECEPTORS

4.1 Picornaviridae

For viruses transmitted in blood or gastrointestinal luminal contents, as in the case of hepatitis A virus (HAV), the initial binding should ideally effect rapid docking of the virus on the host cell. In this case, the binding rate may be more biologically relevant than affinity; thus, a virus might initially bind weakly to an abundant receptor and then, by alternately making and breaking this weaker bond interaction, browse over the cell surface until it finds a second high-affinity receptor.

The recent report by Kaplan and colleagues (1996) represents the first significant step toward successfully identifying the functional receptor that mediates HAV infection. They have identified an attachment

receptor for HAV, termed HAVcr-1, which appears to be a novel mucin-like class-1 integral membrane glycoprotein. This molecule contained a cysteine-rich region with homology to the variable domains of members of the immunoglobulin superfamily. As the HAVcr-1-like mucins appear to be ubiquitous on the cell-surface membrane, a model of a coreceptor or cofactors may be needed to explain the tropism of HAV for hepatocytes. Indeed, the almost universal presence of these mucin-like proteins on cells could itself explain the earlier observations of the ubiquitous nature of binding of HAV to a wide range of cell types.

Previous studies have shown that HAV binds to a wide range of cultured cells in a calcium-dependent manner.

Further characterization of the HAVcr-1, its distribution and interaction with the HAV virion will help us to better comprehend the mechanisms of replication and pathogenesis of this unique picornavirus.

Encephalomyocarditis (EMC) virus belongs to the genus *Cardiovirus* of the *Picornavirus* family. The attachment molecule for EMC virus on human erythrocytes is glycophorin A, the major sialoglycoprotein of the erythrocyte surface membrane, and sialic acid is the residue involved in the virus binding (Allaway *et al.* 1986; Tavakhol and Burness 1990). However, human erythrocytes do not support EMC virus growth, in contrast to a number of human nucleated cells in which the virus readily replicates (Jungeblut and Kodza 1957; McClintock *et al.* 1980; Pardoe *et al.* 1990). Madin-Darby bovine kidney cells do not express glycophorin A and are resistant to the EMC virus infection. However, transfection of the cells with glycophorin A cDNA results in expression of glycophorin on the cell surface, and cells become susceptible to infection with EMC virus (Grewal *et al.* 1991). Vascular cell-adhesion molecule 1 (VCAM-1) has been identified as a receptor for the D strain of EMC virus on murine vascular endothelial cells derived from heart (Huber 1994). Jin *et al.* (1994) identified 70-kDa sialoglycoprotein molecule(s) other than glycophorin A on the surface of HeLa and K562 cell lines serving as EMC receptor.

Members of either the immunoglobulin or integrin superfamily are known to function as receptors for several picornaviruses. The poliovirus receptor (Mendelsohn *et al.* 1989), the major group human rhinovirus receptor (ICAM-1) (Greve *et al.* 1989; Staunton *et al.* 1989; Tomassini *et al.* 1989), and the receptor for the D variant of encephalomyocarditis virus (VCAM-1) (Huber 1994) are all members of the immunoglobulin superfamily. The receptor for echovirus types 1 and 8 has been identified as VLA-2 (Bergelson *et al.* 1992, 1993), and vitronectin receptor has been identified as a receptor for CAV-9 (Roivainen *et al.* 1994). These two receptors belong to the integrin superfamily.

Human enterovirus coxsackievirus A9 has been shown to utilize the vitronectin receptor integrin $\alpha_V\beta_3$ as a receptor on monkey kidney cells (Roivainen *et al.* 1994), although there is evidence that this virus may also utilize a non-RGD-dependent alternative receptor (Roivainen *et al.* 1996).

Foot-and-mouth disease virus (FMDV) (Picornaviridae, *Aphthovirus*) utilize the same receptor on several cell lines as coxsackie A virus (CAV-9) and its conserved integrin-binding RGD motif is essential for infectivity (Berinstein *et al.* 1995). Recent data provide evidence for the role of the vitronectin receptor as an FMDV cell receptor (Sharma *et al.* 1997).

It was suggested that FMDV may use alternative RGD-dependent integrins, since it can bind and replicate in some cells where CAV-9 cannot (Berinstein *et al.* 1995). Furthermore, heparan sulfate has been shown to be required for efficient infection of cells in culture (Jackson *et al.* 1996). Mutant cell lines deficient in heparan sulfate were unable to support plaque formation by FMDV, even though they remained equally susceptible to another picornavirus, the bovine enterovirus.

Echoviruses are nonenveloped single-stranded positive-sense RNA viruses belonging to the *Enterovirus* genus of the Picornaviridae family. They are associated with a range of clinical conditions, including diarrhea, rashes, and most notably viral meningitis, being responsible for about 30 % of cases. The cellular receptors for some enteroviruses have been identified. The receptor for poliovirus is a member of the immunoglobulin superfamily, the function of which is not yet known, and the receptor for echoviruses 1 and 8 is the integrin VLA-2, which normally binds collagen and laminin (Bergelson *et al.* 1992, 1993). Receptors for other picornaviruses have also been identified. These include the intercellular adhesion molecule 1 (ICAM-1) which is the receptor for the major group of human rhinoviruses, and members of the low-density lipoprotein receptor family, which appear to function as receptors for the minor group of human rhinoviruses (Hofer *et al.* 1994). Decay-accelerating factor (DAF) has been identified as a cell receptor for echoviruses 7, 13, 21, 29, and 33 (Bergelson *et al.* 1994). DAF is a member of the RCA (regulator of complement activation) gene family, which plays a role in down-regulation of complement activity at the cell surface (Nicholson-Weller 1982). It interacts with the C3/C5 convertase enzymes, which are critical in both the classical and alternative complement pathways, with the result that the convertases are disassembled and thus inactivated.

Other picornaviruses that are known to be able to use two different receptors in their entry are minor group rhinoviruses (Hofer *et al.* 1994). In cells expressing the low-density lipoprotein receptor (LDLR) this

protein is the receptor for the minor group of rhinoviruses. However, in LDLR-deficient fibroblasts the alternative receptor, α2-macroglobulin receptor, mediates efficiently virus binding and entry.

Xu *et al.* (1994) identified coxsackievirus B3 receptor from mouse brain as a glycoprotein of 46 kDa. Sugar residues were not the direct binding sites for virus, as found for other picornavirus–receptor interactions (Crowell and Tomko 1994).

cDNA clones expressing the murine homolog (mCAR) of the human coxsackievirus and adenovirus receptor (CAR) were isolated. Nonpermissive CHO cells transfected with mCAR cDNA became susceptible to infection by coxsackieviruses B3 and B4 and showed increased susceptibility to adenovirus-mediated gene transfer. These results indicate that the same receptor is responsible for virus interactions with both murine and human cells (Bergelson *et al.* 1998).

The ubiquitous cell-surface molecule DAF is a major cell attachment receptor for coxsackieviruses B1, B3, and B5.

4.2 Alphaviridae

Several investigators have identified potential alphavirus receptor proteins. Helenius *et al.* (1978) suggested that murine and human histocompatibility antigens serve as alphavirus receptors. Ubol and Griffin (1991) identified two proteins of 110 kDa and 74 kDa that may serve the same function on mouse neuronal cells. Wang *et al.* (1992) suggested that the high-affinity laminin receptor functions as a receptor for SIN virus infection of BHK cells.

The Venezuelan equine encephalitis (VEE) virus complex is a group of serologically related alphaviruses. In nature, these viruses are transmitted between susceptible vertebrate hosts by a variety of mosquito species.

The 32-kDa laminin-binding protein from the mosquito *Aedes albopictus* C6/36 cell line is a likely candidate receptor for VEE (Ludwig *et al.* 1996). Other scientists have studied the characteristics of virus attachment to cells without attempting to identify the receptor molecule (Smith and Tignor 1980).

Semliki forest virus enters the host cell by means of receptor-mediated endocytosis. It has been shown that cholesterol in the host-cell or a liposomal membrane is essential for fusion. Cholesterol-depleted cells retain their ability to bind, internalize and acidify the virus but are unable to undergo fusion and subsequent replication. Other alphaviruses examined all appear to need cholesterol for fusion. It has been shown that this strict dependence on cholesterol for SFV fusion in addition requires sphingolipid in the target membrane (Nieva *et al.* 1994). Cholesterol is necessary and sufficient for the low-pH-dependent binding of the virus to the membrane, and the sphingolipid is confined to the actual fusion event. The low amounts needed for half-maximal fusion (10–20 mol/L), indicate that sphingolipids do not play a matrix role but rather are involved in a specific interaction with the fusion peptide.

Laminin-binding proteins are ubiquitous, being found in cells from a variety of organs and tissues. Many forms of laminin-binding proteins with various biochemical characteristics have been identified (for review *see* Mecham 1991). The laminin-binding proteins known as galactoside-binding lectins are of particular interest. These include 12–14-kDa, 31–35-kDa, and 67-kDa antigenically cross-reacting proteins. These represent receptors for SIN, VEE, and probably many other viruses with broad host range.

4.3 Flaviviridae

Japanese encephalitis virus (JEV), a member of the family Flaviviridae, is an important human pathogen that causes encephalitis in southeastern and far-eastern Asia. The entry of flaviviruses into cells occurs by an endocytotic mechanism. However, despite their extraordinary medical importance, receptors for flaviviruses remain unknown. JEV virus has been shown to bind to a 74-kDa molecule on the susceptible VERO cell line without further characterization (Kimura *et al.* 1994).

At present, the best-known structural representative of the family Flaviviridae is the tick-borne encephalitis virus (TBE). The 3-D structure of its glycosylated surface protein E has been established (Rey *et al.* 1995). Its receptor-binding domain has the topology of the immunoglobulin superfamily proteins, being a constant-type fold (Bork *et al.* 1994). This is the first visualization of an Ig-like domain in a viral structural protein. As there is considerable conservation of the amino acid sequence of the E protein across the flaviviruses, biological information from other viruses can be directly mapped to the TBE virus structure.

Structurally, the glycoproteins of flaviviruses are obviously quite different from either influenza HA or alphavirus spikes. However, when they are triggered to penetrate a host cell, similarities emerge. Recent studies have shown that low pH causes the E homodimers to rearrange into homotrimeric assemblies (Rey *et al.* 1995).

Although the receptors for flaviviruses have not been identified, there is a remarkable RGD insertion in the FG loop of mosquito-borne flaviviruses, a characteristic motif of ligands for certain members of the integrin family of cell-surface receptors. We believe that this RGD motif plays a role in virus molecular ecology. Mosquito-borne viruses can be transmitted by ticks as well.

Several attempts have been undertaken to identify TBE receptors. 'Anti-idiotype' polyclonal antibodies immunoprecipitated a 110-kDa protein from porcine kidney embryo cells, that Maldov *et al.* (1992) believed to be fibronectin. Virus overlay assays as well as monoclonal anti-idiotype antibodies were used by our group to approach this problem. Both techniques identified a dimeric molecule of 35-kDa composed of two noncovalently bound 18-kDa subunits on goose erythrocytes as well as on some susceptible cell lines. In addition, monoclonal anti-idiotypic antibodies, which mimic viral epitopes responsible for receptor binding, immunoprecipitated some additional membrane proteins. The anti-idiotypes used protect susceptible cell lines against viral infection *in vitro* and induce antiviral immunity in experimental animals (Kopecky *et al.* 1999).

Human VLA-3 integrin and 67-kDa nonintegrin laminin binding protein were identified as possible receptors for TBE on renal embryonal cells (Protopopova *et al.* 1997).

A 65-kDa protein from susceptible mouse and human neuroblastoma cell lines has been identified as a possible receptor for Dengue 2 virus (Ramos-Castaneda *et al.* 1997).

The bovine viral diarrhea virus (BVDV) is the prototype virus of the genus *Pestivirus*. Pestiviruses are pathogens of great economical importance for the farming industry. They infect pigs, sheep, cattle and a wide range of wild living even-toed ungulates. Multiple attachment sites for BVDV on bovine cells were identified using anti-idiotypic antibodies (Schelp *et al.* 1995).

Hepatitis C virus (HCV) is a causative agents of chronic human infection. The HCV envelope protein E2 binds human CD81, a tetraspanin expressed on various cell types including hepatocytes and B lymphocytes. Binding of E2 was mapped to the major extracellular loop of CD81. Recombinant molecules containing this loop bound HCV and antibodies that neutralize HCV infection *in vivo* inhibited virus binding to CD81 *in vitro* (Pileri *et al.* 1998).

4.4 Coronaviridae

Substantial progress has been made in the identification of molecules used by coronaviruses for gaining entry into cells. Several glycoproteins of the murine carcinoembryonic antigen family have been reported to be functional receptors for mouse hepatitis virus porcine enteric coronavirus (Williams *et al.* 1991; Yokomori and Lai 1992). The transmissible gastroenteritis virus (TGEV) and human respiratory coronavirus 229E both utilize a membrane-bound metalloproteinase, the aminopeptidase N, as specific receptor (Delmas *et al.* 1992; Yeager *et al.* 1992).

Porcine and human coronaviruses utilize aminopeptidase N as receptor but in a species-specific manner. Mouse hepatitis virus uses several rodent glycoproteins in the CEA family as receptors. In addition, some coronaviruses can interact with saccharide moieties on the cell surface.

Sialic acid has been shown to serve as a ligand for binding of TGEV to erythrocytes. The virus is able to recognize N-acetylneuraminic acid but more efficient binding to receptors containing another type of sialic acid, N-glycolylneuraminic acid, was observed (Schultze *et al.* 1996). The biological importance of sialic-acid-binding activity is not known. Interestingly, a related virus, porcine respiratory coronavirus, lacks HA activity. Coronaviruses like TGEV are exceptional among enterotropic viruses because they contain a lipid envelope. Both TGEV and PRCV grow well in cell culture with aminopeptidase N as receptor (Delmas *et al.* 1992, 1993).

Murine coronaviruses, such as mouse hepatitis virus (MHV) infect mouse cells *via* cellular receptors that are isoforms of biliary glycoprotein (Bgp) of the carcinoembryonic antigen gene family. The Bgp isoforms are generated through alternative splicing of the mouse *Bgp1* gene that has two allelic forms called MHVR (or mmCGM1), expressed in MHV-susceptible mouse strains, and mmCGM2, expressed in SJL/J mice, which are resistant to MHV (Dveksler *et al.* 1991, 1993). The Bgp2 member of the same family of glycoproteins has been shown to function as a less efficient receptor for MHV (Nédellec *et al.* 1994). CEA-related glycoproteins are expressed on epithelial surfaces of the gastroenteric and respiratory tracts, which are major portals for entry of viruses and other pathogens. There is a great variety of CEA-related glycoproteins which are expressed by complex splicing patterns from many closely related genes. Given the complex, temporally regulated, and tissue-specific patterns of expression of the many similar CEA-related murine glycoproteins, defining the number of isoforms that can serve as MHV receptors and determining their roles in virus infection *in vivo* constitute an exciting challenge.

Bovine coronavirus isolates studied in some detail agglutinate erythrocytes of rodents and thus belong to the hemagglutinating coronaviruses. Uniquely, the envelope of these coronaviruses has three glycoproteins. Acetylesterase activity is associated with E3 hemagglutinin (Vlasak *et al.* 1988). This virus penetrates its host cell by direct fusion with the plasmalemma and does not require an acidic intracellular compartment for infectious entry (Payne *et al.* 1990).

4.5 Filoviridae

Ebola, Marburg and Reston viruses are the members of the Filoviridae family of negative-strand RNA viruses with non-segmented genomes (Mononegavirales) besides the Paramyxoviridae and Rhabdoviridae. Becker *et al.* (1995) observed that the asialoglycoprotein-receptor may serve as a primary receptor for Marburg virus in the liver, the main target organ for infection. Remarkably, binding of virus to hepatocyte cells was calcium-dependent. From their data it cannot be ruled out that a second, minor, receptor exists in hepatocytes, a receptor that may not necessarily be tissue-specific. Several cell lines and endothelial cells which lack the asialoglycoprotein receptor are able to support viral growth (Schnittler *et al.* 1993).

4.6 Rhabdoviridae

Although binding of rabies virus to the α-subunit of the muscle-type nicotinic acetylcholine receptor (AchR) has been demonstrated (Gastka *et al.* 1996), it remains unknown whether the AChR is an essential host-cell receptor *in vivo*. Other components of the cell surface might act as rabies virus receptors. These constituents include phospholipids or glycolipids, gangliosides, sialic acid and other saccharides. In BHK-21 cells, the VOPBA showed specific rabies virus binding to a high-molar-mass "fibronectin-like" protein as well as at least four other proteins migrating between 66 and 200 kDa (Broughan and Wunner 1995). Rabies viruses probably utilize several types of cell receptors.

4.7 Paramyxoviridae

Worldwide, measles is still a life-threatening disease, causing almost two million human deaths per year. The tropism of measles virus (MV) (Paramyxoviridae, *Morbillivirus*) is widespread, leading to infection not only of epithelial cells of the respiratory tract and peripheral blood mononuclear cells but also of endothelial cells and cells in various organs, including the central nervous system. Studies in the past have suggested that the cell receptors for MV might be functionally associated with the substance-P receptor (Harrowe *et al.* 1990, 1992) or the acetylcholine receptor (Yoshikawa *et al.* 1991). Two cell surface molecules, CD46 (Doring *et al.* 1993; Naniche *et al.* 1993) and moesin (Dunster *et al.* 1994), have been identified to be functionally associated with MV susceptibility. CD46 (membrane cofactor protein) is a classical transmembrane protein binding the complement proteins C3b and C4b and inhibiting complement lysis of host cells. The other putative receptor molecule, the membrane-organizing external spike protein, moesin, a member of the ERM (ezrin, radixin, moesin) family of proteins was characterized as a heparin-binding protein which is localized mainly at the inner, but also at the outer, surface of the plasma membrane (Lankes and Furthmayer 1991; Lankes *et al.* 1988). The CD46–moesin complex is functionally involved in the uptake of MV into cells. Monoclonal antibodies against both constituents efficiently block infection with MV, but not with viruses as closely related as canine distemper virus in tissue culture.

Although CD46 would appear to be the cell receptor for vaccine strains of MV, recently there has been an accumulation of data suggesting that CD46 does not play this role for MV wild-type strains (reviewed in Buckland and Wild 1997).

Sendai virus, an enveloped paramyxovirus, possesses two surface glycoproteins, hemagglutinin–neuraminidase (HN) and the fusion protein (F). The virus fuses with the host-cell plasma membrane in a pH-independent way. It is likely that receptor binding by HN causes a conformational change that activates the F protein (Dallocchio *et al.* 1995). The following multistep mechanism was proposed for paramyxovirus entry into host cells. HN binds to the sialic acid receptor and undergoes a conformational change, to expose an allosteric site. This binds to F, resulting in the inhibition of neuraminidase and in strengthening of virus–cell binding. By interacting with HN, F undergoes a conformational change, exposing the N-terminal fusion peptide. Thus, the receptor-induced interaction of HN and F according to this model is analogous to the low-pH-induced conformational change undergone by influenza hemagglutinin.

Using phospholipid liposomes and fusion with Sendai virus, it has been shown that fusion is particularly sensitive to the presence of ganglioside GD1a (Epand *et al.* 1995).

4.8 Orthomyxoviridae

Influenza virus hemagglutinin (HA) is the viral surface glycoprotein responsible for host-cell attachment and membrane fusion. The molecule is trimeric and characterized by a long, triple-helical coiled coil that supports the globular lectin domains responsible for binding sialic acid-containing cell-surface receptors. X-ray crystal structures of the HA in complex with sialyllactose and several synthetic sialic acid derivatives (Sauter *et al.* 1992; Weis *et al.* 1988) have defined two (α-2,3) sialyllactose-binding sites on each monomer that result in a three-fold symmetric array of six potential receptor-binding sites. Subunit multivalency is likely to play an important role in HA function.

There exist three types of influenza virus, A, B and C. The ssRNA genome of type A and B virus encodes two surface glycoproteins, neuraminidase (NA) and hemagglutinin (HA), which interact with the same sugar, sialic (or neuraminic) acid. HA binding to sialic acid on the surface of the target cell is the first step of infection. NA hydrolyzes the terminal glycosidic bond of sialylated cell-surface glycoproteins, yielding free sialic acid. This process is thought to be important for the release of the virus from the cell surface and thus for propagation of the infection (Air and Laver 1989).

The second glycoprotein spike on the virus is neuraminidase. The role of the essential viral enzyme may be to prevent viral aggregates by removing sialic acid from the virus envelope. Alternatively, it may release newly assembled virus particles from the cell surface, or remove sialic acids from, for example, mucin to lower the viscosity and allow the virus to reach the epithelial cells.

An influenza virus A mutant that lacks neuraminidase activity has been shown to be infectious in cell cultures and when administered intranasally to mice (Liu *et al.* 1995). Formation of viral aggregates in the cell culture, which could be prevented by adding enzyme, was the only defect of the mutant that could be demonstrated.

NA, a homotetrameric 240-kDa molecule, consists of a box-like head which is anchored to the virion membrane by a stalk.

Influenza A and influenza B NA share less than 25 % sequence identity in the head region, yet the overall structures of the two enzymes are very similar. Also, the architecture of the active-site pocket and the binding mode of sialic acid are very well conserved, so that X-ray crystallographic studies on both viruses reached the same conclusions (Varghese *et al.* 1983, 1992; Baker *et al.* 1987; Burmeister *et al.* 1992). Despite knowledge of the structures of the sialic acid complexes, the enzymic mechanism of NA remains unclear.

The crystal structure of the complex with sialyllactose, reported by Wiley and co-workers in 1988, defined the conserved and retracted receptor-binding site as being too narrow to be accessible for recognition by immunoglobulin molecules.

With the ultimate aim of designing effective inhibitors of viral attachment, four high-affinity sialic acid analogs were determined in complex with hemagglutinin (Watowich *et al.* 1994).

Binding to sialylated cell-surface receptors is a prerequisite for viral infection *via* fusion with the host cell membrane at the low pH of the endosome. However, the structures referred to cannot explain this phenomenon. The trimeric spikes that carry at their tips the receptor-binding sites have a length of 13.5 nm, which would seem to disqualify the membranes from any closer approach. Furthermore, the fusion peptide, which is assumed to insert into the host membrane, is located 10 nm from the distal tip and 3.5 nm from the viral membrane, and is buried in the spike.

The atomic structure of a soluble fragment of the low-pH form of the hemagglutinin shows a massive rearrangement, compared with the high-pH form, involving movement of the N terminus of the hemagglutinin some 10 nm towards the target membrane (Bullough *et al.* 1994). However, hemagglutinin in this changed conformation still holds the two viral and host-cell membranes about 10 nm apart. A study by Gyu *et al.* (1994) suggests that the long coiled-coil trimer of hemagglutinin may insert into membranes; further rearrangement of the peptide through melting into the lipid bilayer may finally bring the two membranes together and facilitate fusion.

Huang *et al.* (1996) reported annexin V (33 kDa) to be needed for influenza A and B virus infectivity, probably as a second receptor. The hemagglutinin binds to the first receptor, sialic acid, when the virus initially encounters the cell. Reaction with annexin probably occurs after the virus is drawn to its proximity by sialic acid. Annexins have been reported to fuse membranes at neutral pH. This occurs by a different mechanism than the acid-triggered fusion mediated by influenza virus hemagglutinin. It is of interest that hepatitis B virus and human cytomegalovirus have also been shown to use annexins as receptors.

Different virus variants have acquired a substrate specificity complementary to the hemagglutinin receptor specificity, with a parallel drift through evolution. Human influenza B virus isolates investigated during the period 1940–90 demonstrated a successive shift in preference toward a sialyl-6 over a sialyl-3 linkage in glycolipids, both for hemagglutinin and sialidase (Xu *et al.* 1994).

In the case of influenza C virus, the hemagglutinin receptor is 9-O-acetyl-Neu5Ac, and the enzyme is an esterase. Madin-Darby canine kidney cells, which are resistant to infection, were made sensitive by enzymic transfer of 9-O-acetyl-Neu5Ac. However, transfer of the receptor analog (9-thioacetamido-Neu5Ac) did not result in infection but only in binding (Brossmer *et al.* 1993). The investigators concluded that the receptor-destroying enzyme plays an important role at the post-adsorption stage of the infection for this virus, possibly facilitating virus transfer from glycoproteins to glycolipids to afford closer contact between viral and host-cell membranes. Polyglycosylceramides, complex glycolipids containing up to 50 or more sugar residues, are recognized as the minor components of the cell surface membranes. However, a knowledge on their tissue distribution, structure and function is limited. The identity of the biological receptors for influenza viruses on the target cells, be they glycoproteins or glycolipids, nevertheless remains unknown. Preparations of polyglucosylceramides from human erythrocytes were found to support binding of A and B influenza virus strains at a much lower concentration than sialyl-6-paragloboside and to be somewhat better receptors for these viruses compared to the sialylglycoprotein, fetuin (Matrosovitch *et al.* 1996).

Fusion peptides structurally related to that of influenza HA are found in many other viral fusion proteins, including the F protein of Sendai virus (a parainfluenza virus), the E-protein complex of Semliki forest virus, and gp41 of human immunodeficiency virus. A putative fusion peptide is also present in PH-30, a protein involved in sperm-egg fusion. Putative fusion domains in the envelope glycoprotein of rabies and vesicular stomatitis viruses have been identified (Durrer *et al.* 1995). Although there are obvious parallels in the behavior of rhabdovirus glycoprotein and influenza virus HA, it is also important to refer to striking difference that may be relevant in defining viral fusion mechanisms. In the case of rhabdoviruses, the conformational changes from the native toward the active and inactive conformation at low pH are completely reversible after readjusting the pH to above 7.0.

An advanced knowledge about host cells receptors for influenza viruses help to explain the emergence of pandemic influenza viruses. Ito *et al.* (1998) showed that some avian-like swine influenza viruses acquired ability to recognize human virus receptors, raising the possibility of their direct transmission to human populations.

4.9 Reoviridae

Rotaviruses belong to the Reoviridae family. These nonenveloped viruses have a complex icosahedral structure with two protein capsids and an inner core containing a segmented double-stranded RNA genome. The mechanisms of rotavirus binding and penetration into cells are not fully understood. Attempts to identify rotavirus receptors have been made. Binding studies have revealed the presence of at least two families of putative receptors: one sialic-acid-dependent, for animal rotaviruses, the other sialic-acid-independent, for human rotaviruses (Fukudome *et al.* 1989; Keljo and Smith 1988; Mendez *et al.* 1993; Svensson 1992; Yolken *et al.* 1987). Rhesus rotavirus seems to bind to a large sialic acid-containing glycoprotein of brush-border membranes from suckling-mice enterocytes (Bass *et al.* 1991). The interaction between enveloped virions and biological membranes is believed to involve fusion between the lipid phases of both membranes. Such fusion, however, cannot take place with rotaviruses, which lack a lipid membrane. Rather, rotavirus–membrane interactions may be expected to involve only the readily exposed proteins of the outer capside and either the membrane lipids, membrane proteins, or both. Viral protein–membrane interactions have been shown to occur between rotaviruses and membrane glycosphingolipids (Willoughby *et al.* 1990) and between rotaviruses and liposomes (Nandi *et al.* 1992). Lipid composition, presence or absence of membrane proteins, may determine the kinetics of virus–membrane interactions. Protein–protein interactions of the ligand–receptor type have been found in African green monkey kidney cells and in murine enterocytes. Ruiz *et al.* (1994) suggested that rotaviruses are capable of bypassing the membrane protein receptor to interact directly with membrane lipids in the different types of membranes assayed. Strong evidence that specific receptors can be bypassed has been presented by Mendez *et al.* (1993). They have shown the existence of at least two sites on the VP4 protein of animal rotaviruses: a sialic-acid-binding site in the VP8 moiety, and a sialic-acid-independent site that might involve the fusion peptide within VP5 (VP5 and VP8 are cleavage products of VP4). The first binding reaction is not necessary for infection, as demonstrated by the isolation by these workers of sialic-acid-independent mutants in which the interaction of VP8 with the membrane receptor can in fact be bypassed.

However, like the wild-type viruses, the mutants were able to hemagglutinate in a sialic-acid-dependent manner, which was inhibited by adding sialidase or glycophorin. Several membrane glycoconjugates that contain sialic acid have been proposed as binding sites for animal rotaviruses in epithelial cells; however, human rotaviruses are not dependent for their binding on the presence of sialic acids on target cells.

Both human and animal rotaviruses have been shown to bind to non-acid glycolipids, including ganglioside GgO4. Asialo-GM1 mediates the binding of rotavirus to polarized epithelial cells (Srnka *et al.* 1992).

Rotavirus binding and entry is evidently a complex phenomenon that is still poorly understood.

4.10 Retroviridae

Lentiviral infections have a number of clinical features in common: long incubation periods, persistence in the face of vigorous immune responses, multiorgan disease, and an invariably fatal outcome. The lentiviruses can be divided into two groups on the basis of their tropism for different host cells. Equine infectious anemia virus, the ovine lentiviruses (including ovine progressive pneumonia viruses and maedi-visna virus), and the caprine lentiviruses (caprine arthritis–encephalitis virus) replicate predominantly in macrophages. In contrast, the human, simian, and feline viruses replicate in both lymphocytes and macrophages. This difference in cell tropism is responsible for the differing disease manifestations of these two virus groups.

In their natural hosts the simian lentiviruses appear to be relatively nonpathogenic; however, transfer of these viruses to other species naturally free of the virus results in disease. This has been observed previously with the epidemic of maedi-visna disease in Iceland after the introduction of foreign sheep and may also account for the emergence of AIDS in Africa. This is supported by the genetic relationship of the HIV-2 to SIV_{mac} and SIV_{sm} isolates and of HIV-1 to the SIV_{cpz} isolates (Hirsch and Johnson 1994). Lentiviruses can be relatively nonpathogenic in their natural hosts, as evidenced by widespread infections of nonhuman African primates with strains of SIV and worldwide infections of goats and sheep with lentiviruses. Lentiviral infections do not always result in clinically evident diseases, and diseases, when manifested, have long incubation periods. Thus, it is conceivable that there are other species that harbor specific lentiviruses, and these may be the causative agents for other chronic-progressive disease syndromes.

One exception to the relative species specificity of the lentiviruses is the bovine immunodeficiency virus. Rabbit and mouse models have been established for bovine immunodeficiency virus-induced disease (Gonda *et al.* 1994; Pifat *et al.* 1992).

Several retroviral receptors have been identified to date. The receptors for human and simian immunodeficiency viruses CD4 (Dalgleish *et al.* 1984; Klatzmann *et al.* 1984; Sattentau *et al.* 1988), avian leukosis virus type A, Tva1 (Young *et al.* 1993), and bovine leukemia virus Blvr (Ban *et al.* 1993) are organized with a hydrophilic globular extracellular domain linked to an intracellular portion by a single membrane-spanning sequence. Receptors for feline immunodeficiency virus, CD9 (Hosie *et al.* 1993), ecotropic murine leukemia viruses MCAT (Albritton *et al.* 1989), amphotropic murine leukemia viruses Ram-1, Pit-2 (Miller *et al.* 1994; van Zeijl *et al.* 1994), and the common receptor, Glvr-1, Pit-1 for gibbon ape-leukemia virus, GaLV (O'Hara *et al.* 1990), feline leukemia virus group B (Takeuchi *et al.* 1992), and simian sarcoma-associated virus (Sommerfelt and Weiss 1990) span the cell membrane several times. Mcat, Glvr-1, and Ram-1 are transport proteins, with MCAT serving as a cationic amino acid transporter (Kim *et al.* 1991; Wang *et al.* 1991), while Ram-1 and Glvr-1 are both sodium-dependent phosphate symporters (Kavanaugh *et al.* 1994).

The gene encoding the cell receptor for subgroup A avian leukosis and sarcoma viruses has been cloned from chicken and quail cells (Bates *et al.* 1993; Young *et al.* 1993). The extracellular domain of the ALSV-A receptor contains a region that is related in sequence to the seven ligand-binding domains of the low-density lipoprotein receptor.

The major cell receptor for primate lentiviruses is the CD4 molecule on the surface of T lymphocytes and monocytes/macrophages. Galactosylceramide has been identified as a potential receptor for HIV-1 in cells derived from the central nervous system (Bhat *et al.* 1992; Harouse *et al.* 1989). Identification of receptors for other lentiviruses is still tentative. Two reports have identified putative receptors for maedi-visna virus, one suggesting that sheep class II histocompatibility antigen may be involved in virus–cell interaction and the other identifying a cell surface molecule of 50 kDa (Crane *et al.* 1991; Dalziel *et al.* 1991).

In addition, cell factors play a crucial role in the post-binding steps since there is a host restriction observed for many lentiviruses at this stage. Despite the introduction of the human CD4 gene into mouse cells, HIV-1 is unable to infect such cells.

The ability of lentiviruses to replicate in nondividing cells distinguishes them from other groups of retroviruses. In all of the lentiviruses, productive replication in macrophages is linked to cell maturation. Promonocytes and monocytes in the bone marrow and blood are infected, but viral replication in these cells is restricted and the virus remains in the form of proviral DNA. Upon maturation and differentiation to macrophages, either in tissue or in cell culture, cell transcriptional factors that initiate viral transcription and subsequent production of viral proteins and virions are produced (Anderson *et al.* 1983; Narayan *et al.* 1983).

Myers and Lenroot (1992) note that the amino acid sequence of the external Env protein of HIV-1 (gp120) ranks fourth in the density of potential N-glycosylation sites, among some 10 000 glycoprotein

sequences in the SWISS-PROT library. In the gp120 of studied HIV isolates these sites are all occupied (Mizuochi *et al.* 1988, 1990; Geyer *et al.* 1988; Holschbach *et al.* 1990; Leonard *et al.* 1990). It has been argued that glycosylation of gp120 is essential for folding of the glycoprotein but not for its binding to CD4 (Bahraoui *et al.* 1992; Li *et al.* 1993; Fenouillet *et al.* 1993, 1994). HIV should be a likely target for interaction with lectins *via* its conjugated saccharides. It has been suggested that a 'postbinding event' is involved in the neutralization obtained with mannose-specific lectins (Balzarini *et al.* 1991; Gattegno *et al.* 1992). Alternatively, the lectin may affect membrane fluidity and fusion capability by capping phenomena. Whereas other mitogenic lectins such as PHA and WGA may enhance expression of HIV provirus or virus-induced syncytium formation, GNA acts in the opposite direction and blocks infection.

HIV infection is inhibited by monoclonal antibodies recognizing diverse cell surface antigens including CD4, CD7, MHC class I and II, LFA-1 and ICAM-3. However, there appear to be several distinct mechanisms by which such antibodies achieve their inhibitory effect. Inhibition of virus entry may be mediated by direct neutralization of the virus, as with antibodies against MHC II. This phenomenon is thought to be the result of incorporation of cell antigens into the viral envelope as the virus buds from the cells (Arthur *et al.* 1992). An alternative mechanism by which antibodies against cell surface antigens may inhibit infection involves binding of the antibody to the virus receptor CD4, co-receptors such as LESTR (Feng *et al.* 1996), or to cell membrane proteins involved in the process of cell-cell fusion (Braun *et al.* 1995). Antibodies recognizing the CDR3 domain of CD4, the primary receptor for HIV, inhibit HIV infection at the level of transcription but do not prevent virus entry (Benkirane *et al.* 1993).

A monoclonal antibody which blocks infection with feline immunodeficiency virus was found to react with the cell surface molecule CD9, implicating CD9 in the process of virus entry (Willett *et al.* 1994). Recently, the same authors demonstrated that the inhibition of FIV infection by anti-CD9 antibody operates after virus entry and is independent of virus tropism, subtype and passage history (Willett *et al.* 1997).

Ecotropic retroviruses are able to infect only rodent cells, while amphotropic retroviruses can infect cells from many species. Xenotropic retroviruses are usually unable to infect mouse cell lines, but can infect cells of other species. Polytropic viruses are the product of recombination events between ecotropic viruses and endogenous mouse proviral sequences (Chattopadhyay *et al.* 1981; Fischinger *et al.* 1975; Hartley *et al.* 1977) and are able to infect nonrodent as well as most rodent cell lines.

The amphotropic murine retrovirus receptor Ram-1 shows significant sequence similarity to the gibbon ape-leukemia virus (GaLV) receptor Glvr-1, and both of these cell surface proteins normally function as sodium-dependent phosphate symporters. However, Ram-1 from humans of rats does not serve as a receptor for GaLV, and Glvr from humans does not serve as a receptor for amphotropic virus. Murine retrovirus 10A1 has been shown to enter cells by using either Glvr-1 or Ram-1, providing a molecular explanation for nonreciprocal interference between 10A1 and amphotropic viruses (Miller and Miller 1994). In addition, these authors have also constructed hybrid molecules between Glvr-1 and Ram-1 to study determinants required for virus entry and have found that some hybrids can serve as receptors for both amphotropic and GaLV pseudotype retroviral vectors, supporting the hypothesis that retroviruses can use alternative receptors in different cell types. These results provide insight into the evolution of new retrovirus classes with altered host range and receptor utilization. However, their results also complicate retrovirus classification. For example, viruses that use Ram-1 and/or Glvr-1 might all be grouped together or each could define its own group as a result of minor differences in receptor utilization.

Chinese hamster lung cell line E36 exhibits an overlap in GaLV and amphotropic murine leukemia virus (A-MuLV) receptor utilization. Cells infected by GaLV are resistant to superinfection by not only GaLV but also A-MuLV (Eglitis *et al.* 1993). This finding led to the determination that E36 cells express a form of the A-MuLV receptor (termed EAR) which can facilitate infection by not only A-MuLV but also 10A1 MuLV and GaLV (Wilson *et al.* 1994). This receptor is similar to the A-MuLV receptors isolated from human and rat cells and also shares homology with the human GaLV receptor, Glvr1. In addition, it is a functional Na-phosphate symporter (Wilson *et al.* 1995). Viral infection of cells expressing Glvr1 and EAR results in a complete blockade of viral receptor-mediated phosphate transport, yet there is no apparent cytopathology.

CHO K1 hamster cells have been demonstrated to possess a form of the A-MuLV receptor that is inactivated by N-linked glycosylation. This receptor can be rendered functional by pretreating CHO K1 cells with tunicamycin before exposing them to A-MuLVs (Miller and Miller 1992). The presence of this N-linked glycosylation site suggests that cell-specific glycosylation properties may account for the resistance of CHO K1 cells to A-MuLV infection.

A still unexplained phenomenon is the recognition in several viruses of common bilayer-linked epitopes of membrane lipids, notably galactosylceramide (Galβ1,1Cer). One should carefully consider these findings in relation to membrane–membrane fusion and penetration phenomena. It was reported that several

$CD4^-$ cell lines derived from the nervous system (Bhat *et al.* 1991) or colon (Fantini *et al.* 1993) can be infected by HIV-1, and that this infection could be blocked by anti-Galβ1,1Cer antibodies. In solid-phase assays using cell glycolipids only 3-sulfated galactosyl- and lactosylceramide were positive binders of gp120 (Furuta *et al.* 1994). HIV-1 is able to infect cells in a CD4-independent way. Infection may be mediated by binding epitopes within simple sphingolipids which lie close to the bilayer and which possibly facilitate membrane–membrane fusion. In this respect, it is interesting that a number of other viruses bind to Galβ1,1Cer, and to other simple glycolipids, when the virus is suspended on thin-layer chromatograms with separated glycolipids (Karlsson *et al.* 1992). This property was described as an essential second-step binding to position the viral particle close to the host membrane for penetration. The 'classical' receptor, be it a peptide or sugar, then acts as a first-step receptor in selecting a target cell. The events that lead to fusion of the retrovirus envelope with cell membranes are not yet clear. Most retroviruses studied can fuse with cell membranes at neutral pH, so the mode of entry does not depend on receptor-mediated endocytosis *via* acidic endosomes (Weiss 1993).

The conformational changes undergone by gp120–gp41 which lead to membrane fusion, are highly cooperative and require both receptor and coreceptor (Jones *et al.* 1998).

It has been shown that the CCR8 receptor can serve as a coreceptor for diverse T-cell-tropic, dual tropic, and M-tropic HIV-1 strains (Horuk *et al.* 1998).

CXCR-4 is expressed by primary macrophages and functions as a cofactor for entry by dual tropic but not T-tropic HIV-1 isolates (Yi *et al.* 1998).

Identification of genetic polymorphism helps explain why some people, with alterations in the CCR5 gene that prevent expression, are protected from HIV-1 infection (Broder and Collman 1997).

HIV-1 enters its target cells by fusion at the plasma membrane. The primary cell receptor for HIV is CD4 but this molecule is insufficient to permit viral fusion. During 1996, the necessary entry cofactors (coreceptors or second receptors) were identified as members of the seven-transmembrane-spanning G-coupled receptor family fusin: CXCR4 for T-tropic strains and CCR5, principally, for M-tropic strains. The coreceptor functions of these proteins are inhibited by their natural α- and β-chemokine ligands (Moore *et al.* 1997).

4.11 Hepadnaviridae

Several candidate hepatocyte receptors for hepatitis B virus (HBV) have been reported (Hertogs *et al.*1993; Neurath and Strick 1994).

A rat hepatoma cell line, which does not express human annexin V and which is not infectable by HBV, gained the ability to become infected by HBV after transfection with human annexin V.

4.12 Parvoviridae

Replication of parvovirus B19, the only known pathogenic human parvovirus, has been demonstrated only in human erythroid progenitor cells. In the laboratory the virus has been propagated only in bone marrow, peripheral blood, fetal liver, and a few hematopoietic cell lines with erythroid characteristics. The basis for the extraordinary tropism of the virus for erythroid cells has been clarified by the discovery of the cell receptor for this virus (Brown *et al.* 1993). The virus binds to an antigen of the blood-group P system known as P antigen or globoside.

4.13 Papovaviridae

The structure of murine polyoma virus in complex with sialyl-3-lactose has been determined (Stehle *et al.* 1994). Compared with the primary site of influenza virus hemagglutinin, no homology is evident in binding characteristics, and particularly in interaction with galactose. Small plaque strains, which have a broader saccharide-binding capacity, are less pathogenic. The explanation given was that spread in the intact host of the small plaque strains is reduced by the existence of the branched saccharide structures, which may act as non functional receptors only in the case of small plaque virus strains, recently, Evander *et al.* (1997) reported identification of the α_6 integrin as a candidate receptor for papillomaviruses.

4.14 Herpesviridae

Epstein–Barr virus (EBV) is a γ-herpes virus. The two major target cell types for EBV infection are the B and T lymphocytes, in which the infection is largely nonproductive or latent, and stratified squamous epithelium, in which viral replication occurs. EBV enters B lymphocytes following interaction between the

viral membrane glycoprotein gp340/220 and the B-cell receptor for the C3d complement fragment (CD21). Although CD21 can also be the port of entrance for EBV into epithelial cells, an alternative entry route into otherwise resistant epithelial cells is the coupling of virions by EBV-specific polymeric immunoglobulin A to the secretory component, a transmembrane protein expressed by epithelial cells, followed by endocytosis (Gratama and Ernberg 1995).

Penetration of the cell membrane involves a complex of three glycoproteins, gH, gL, and gp42. Glycoprotein gp42 has some features characteristic of members of the C-type lectin gene family and it binds to HLA-DR. Thus EBV uses HLA class II as a cofactor for infection of B lymphocytes (Qingxue *et al.* 1997).

The cell receptor involved in attachment and penetration of herpes simplex virus 1 (HSV-1) into susceptible cells proved to be elusive. HSV encodes at least 13 membrane proteins, of which only 5 glycosylated proteins appear to be required for viral replication in cell cultures. The redundancy of membrane proteins has led to the hypothesis that susceptible cells have multiple receptors interacting with the same or different virion envelope proteins. The initial interaction of HSV with susceptible cells involves a low-affinity binding to cell-surface heparan sulfate glycosaminoglycans mediated by glycoprotein C and probably B. It has been reported that recombinant glycoprotein D binds mannose-phosphate receptors but cell mutants lacking this molecule were susceptible to HSV infection.

Using anti-idiotypic approach, Huang and Campadelli-Fiume (1996) have presented evidence that HSV interacts with cells through glycoprotein D by means of a cell-surface receptor with apparent *M* of 62 kDa, other than the mannose-phosphate receptor. Herpes simplex virus glycoprotein D is required for stable attachment and penetration of the virus into susceptible cells after initial binding.

It has been reported recently that CD4 is a major component of the receptor for human herpesvirus-7, which has been newly identified as a T-lymphotropic virus (Yasukawa 1998).

The cell receptor for human cytomegalovirus (HCMV) entry has not been identified. To date heparan sulfate proteoglycan, annexin II, and CD 13 (aminopeptidase N) are reported to be associated with HCMV entry into human fibroblast cells. However, HCMV appears to enter into neuroectodermal tissue-derived cells *via* a CD 13 independent pathway (Watanabe 1998).

4.15 ASFV

African swine fever virus (ASFV) is an enveloped icosahedral DNA virus responsible for a devastating disease of swine. Its unique molecular properties have led to the establishment of a yet unnamed new family, of which ASFV is the only representative. The virus shows a strict host-range and cell tropism in natural infections, replicating in mononuclear phagocytes and in a small fraction of polymorphonuclear leukocytes. However, the virus has been adapted to grow in several established cell lines from pigs and other animal species (Vinuela 1987). Binding experiments of labeled virus particles to cells have shown the presence of saturable binding sites for virus attachment on the plasma membrane of Vero cells and swine macrophages. ASFV binding to virus-resistant cells and rabbit macrophages was not mediated by saturable binding sites (Alcamí *et al.* 1989, 1990). Although the interaction with rabbit macrophages was not mediated by receptors, the virus penetrated into these cells and initiated abortive infection. Viral attachment protein p12 was identified and sequenced (Angulo *et al.* 1993). It was speculated that p12 and β-chain of integrins share a common structural motif. However, cell receptors remain unidentified.

Surprisingly, antisera raised against p12 did not reduce virus infectivity in an *in vitro* assay. Gómez-Puertas *et al.* (1996) have shown that antibodies to p72 and p54 are involved in the inhibition of a first step of the replication cycle related to virus attachment, while antibodies to p30 are implicated in the inhibition of virus internalization.

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