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Review

Virus receptors in the human central nervous system

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The initial event in the life cycle of a virus is its interaction with receptors present on the surface of a cell. Understanding these interactions is important to our understanding of viral tropism, spread, and pathogenesis. This is particularly true of viruses that target the central nervous system as these viruses must maintain a tropism for both the nervous system and for peripheral organs that allow for viral replication and spread to new susceptible hosts. These viruses therefore interact with a diverse set of cells and tissues, interactions that are likely mediated by both common and unique receptors present on each target tissue. In addition, physiological changes in the host can lead to increased or decreased expression of virus receptors, which influence virus trafficking, spread, and tissue specific pathology. This review will focus on the relatively few virus receptor systems that have been described in some level of detail for viruses that target the human central nervous system. *Journal of NeuroVirology* (2001) **7,** 187–195.

Introduction

The central nervous system (CNS) is a target for a large number of viral infections. The major viruses associated with CNS infection include members of the Picornaviridae (enteroviruses, coxsackieviruses, echoviruses), Paramyxoviridae (measles virus, mumps virus), Herpesviridae (simplex viruses, cytomegalovirus, HHV-6), Togaviridae (Eastern, Western, and Venezuelan Equine Encephalitis viruses), Flaviviridae (Yellow Fever virus, West Nile fever virus, Dengue viruses, Japanese Encephalitis virus, St. Louis Encephalitis virus), Rhabdoviridae (rabies), Arenaviridae (many species), Bunyaviridae (LaCrosse virus, California encephalitis virus), Reoviridae (coltivirus), Retroviridae (HIV-1, HTLV-1), and Papovaviridae (JC Virus) families (for a complete review see (Johnson, 1998). Cell surface receptors for most of the viruses listed here have not been described. This review focuses on those viruses for which specific cell surface receptors have been elucidated or at least partially described.

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Cellular receptors for measles virus

Measles virus (MV) belongs to the family Paramyxoviridae and the genus morbillivirus. Infection with Measles virus (MV) continues to be a major cause of morbidity and mortality worldwide (Griffin and Bellini, 1996). Measles virus infection is usually associated with an acute respiratory illness that is complicated by immune suppression (McChesney and Oldstone, 1989). Measles is also a neurotropic virus that causes acute encephalitis and a slowly progressing chronic disease known as subacute sclerosing panencephalitis (SSPE) (Griffin and Bellini, 1996).

The host range of MV is restricted to humans and to some species of monkey (Blake and Trask, 1921). The limited host range is largely determined by host cell receptor recognition, as MV will not bind to, or infect cells from nonpermissive hosts. Two viral proteins are involved in MV cell entry. The hemagglutinin protein (H) mediates MV attachment to host cell receptors and the fusion protein (F) mediates the fusion of viral and host cell membranes in a pH-independent manner (Wild *et al*, 1991).

Early attempts to identify the specific measles virus receptor on host cells used anti-idiotypic antibodies prepared against H protein to immunopreciptate 20-kd and 30.5-kd proteins from monkey kidney cells (Krah and Choppin, 1988). The identity of these proteins is not known. More recently, a monoclonal antibody raised against Jurkat T cells was found to block

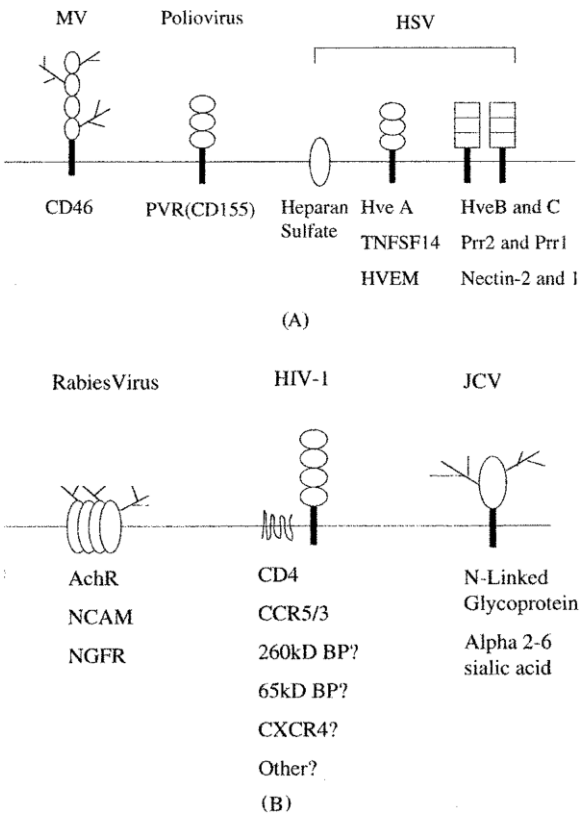

Figure 1A and B Receptors for neurotropic viruses. (A) Measles virus (MV) uses all four isoforms of CD46 to infect cells. All three serotypes of human poliovirus use CD155 (PVR) to infect cells. Herpes Simplex Viruses (HSV) first attach to cells by an interaction of viral glycoprotein C and heparan sulfate. Viral glycoprotein D then interacts with either Herpesvirus entry mediators A, B, or C (HveA, HveB, or HveC). Membrane fusion requires the concerted action of viral glycoproteins gB, gD, gH, and gL. (B) Rabies virus can use either the acetylcholine receptor, neural cell adnhesion molecule (NCAM), or the low affinity nerve growth factor receptor (NGFR) to infect cells. HIV-1 uses CD4 and either CCR5 or CCR3 to infect microglial cells. The mechanism by which HIV infects CD4 negative glial cells in the CNS is not known. A 260 kD protein and a 65 kD protein present on glial cells may be involved. The human polyomavirus, JCV, uses an unidentified *N*-linked glycoprotein containing terminal α 2-6 linked sialic acids to infect glial cells. For all of the viruses discussed in this review, glycosylation of receptor molecules may influence virus-host cell receptor recognition.

MV binding to and infection of a wide range of human and simian cells that were permissive for measles virus infection (Naniche *et al*, 1993a; Naniche *et al*, 1993b). This antibody was subsequently used to immuopurify a 57–62 kd membrane protein that was identified as membrane cofactor protein (MCP) or CD46 (Naniche *et al*, 1993a; Figure 1). In parallel experiments, MV binding to human/rodent somatic cell hybrids localized the measles virus receptor to human chromosome 1 (Dorig *et al*, 1993). These authors hypothesized that CD46 was a likely candidate for this receptor. They then demonstrated that expression of CD46 in nonpermissive cells rendered the cells susceptible to infection with MV (Dorig *et al*, 1993).

CD46 is a member of the regulators of complement activation (RCA) family of proteins. The members of this gene family cluster on human chromosome 1 at q3.2 (Liszewski *et al*, 1991). The protein functions to inhibit complement deposition on normal host cell surfaces. Several isoforms of CD46 have been described and many of these are differentially expressed on cells and in tissues (Buchholz *et al*, 1996). The four common isoforms all function as receptors for MV (Buchholz *et al*, 1996; Manchester *et al*, 1994; Manchester *et al*, 2000).

The role of CD46 in CNS infection is not clear and several studies have suggested alternative mechanisms of measles virus spread in the CNS. In one study, and alternative isoform of CD46 was detected in the brains of several patients who died of measles infection as well as in normal control brain (Buchholz *et al*, 1996). In another study involving SSPE brains, CD46 was not detected (Ogata *et al*, 1997). Finally, measles virus has clearly been shown capable of direct cell to cell spread in the CNS in a CD46-independent manner (Lawrence *et al*, 2000). These data suggest that CD46 is necessary for the initial establishment of CNS infection and that in certain cell types, such as neurons, that MV continues to spread by direct cell-to-cell contact in the absence of CD46.

Several lines of CD46 transgenic mice have been developed and these are being evaluated as models for measles virus infection (Horvat *et al*, 1996; Rall *et al*, 1997; Blixenkrone-Moller *et al*, 1998; Mrkic *et al*, 1998; Oldstone *et al*, 1999). In one model, measles virus infection appears to recapitulate all aspects of measles infection in humans, including immunosuppression and neurotropism (Oldstone *et al*, 1999).

Cellular receptors for polioviruses

The human polioviruses belong to the enterovirus genus of the family Picornaviridae (Rueckert, 1996). All three serotypes cause disease in humans and humans are the only known reservoir of this virus. Primary replication of poliovirus occurs in oropharyngeal and intestinal epithelial cells. The virus then spreads and replicates in lymphoid organs, including Peyers patch, tonsils, and deep cervical and mesenteric lymph nodes. Secondary multiplication in these organs leads to a secondary viremia and virus then spreads to many additional organ systems, including the nervous system. The primary targets of poliovirus infection in the CNS are motor neurons in the anterior horn of the spinal cord, the medulla, the prefrontal gyrus, and the cerebellum. Spinal poliomyelitis occurs when neurons in the anterior horn of spinal cord are affected and bulbar poliomyelitis occurs when cranial nerves and the medulla become infected. Vaccine strains of poliovirus are attenuated for replication in nervous system tissue but maintain the ability to replicate in the gut. Mutations associated with the attenuated phenotype map to domain VI in the

poliovirus internal ribosome entry site (IRES). This indicates that differential recognition of the IRES element by cell-type specific proteins plays a role in determining the neurotropism of poliovirus. Specific poliovirus receptors also contribute to tropism as infection of nonsusceptible cells by poliovirus can be rescued by transfection of a functional poliovirus receptor (PVR). In addition, many cell types that are resistant to infection with poliovirus virions can be infected by poliovirus RNA.

The receptor for poliovirus was originally identified by screening a HeLa cell cDNA library with an exon-specific probe that recognized human genomic DNA encoding poliovirus receptors (Mendelsohn *et al*, 1989; Tomassini and Colonno, 1986). Nucleotide sequence analysis of the cDNA clone revealed that the poliovirus receptor was a new member of the immunoglobulin receptor superfamily of proteins (Figure 1). The human poliovirus receptor gene is located on chromosome 19q13.1-13.2. The PVR gene encodes a pre-mRNA that is differentially spliced to give rise to 4 different polypeptides (reviewed in (Freistadt *et al*, 1995; Gromeier *et al*, 1995; Leon-Monzon *et al*, 1995). Two of these are cell surface proteins (hPVRα and δ) and two lack the transmembrane domain and are secreted (hPVRβ and hPVRγ). Northern blot analysis of human tissues found that PVR mRNA was widely expressed in human tissues. The development of transgenic mice expressing the human PVR also found that the receptor was expressed in more tissues than were susceptible to poliovirus infection. This indicates that presence of a functional PVR is necessary but not sufficient to mediate poliovirus infection. As the PVR is heavily modified by *N*-linked glycosylation and sialyation it is possible that different glycoforms of the hPVRs are expressed in a tissue- and cell-type specific manner. These differences may contribute to viral tropism and would explain the discrepancies described previously. In support of this, the tropism and spread of a related poliovirus, Theiler's murine encephalomyelitis virus (TMEV), is dependent on host cell glycosylation (Zhou *et al*, 1997). This group of viruses can be subdivided into highly neurovirulent strains (GDVII, and TO), and less neurovirulent strains (BeAn, and DA). The highly neurovirulent viruses rapidly destroy neurons, and kill the host within days. The less neurovirulent viruses establish persistent infections and give rise to chronic demyelination (Zhou *et al*, 1997). The major difference between these strains appears to be in host cell receptor recognition (Zhou *et al*, 1997). The persistent viruses all recognize sialyloligosaccharides as a component of their receptors whereas the highly neurovirulent strains do not. This indicates that cell-type specific differences in glycosylation could profoundly affect the tissue specificity of polioviruses in humans and in transgenic mice.

Cellular receptors for Herpes Simplex Viruses

The Herpes Simplex Viruses (HSV-1 and 2) are alphaherpesviruses in the family Herpesviridae. Alphaherpesviruses are characterized by having a short life cycle, a wide host range, and tissue tropism, and by their ability to establish latency in sensory ganglia (Roizman and Sears, 1996). In addition to infecting epithelial cells and establishing latency in sensory ganglia, HSV-1 is also capable of infecting the central nervous system. HSV-1 has been characterized as having low neuroinvasivness but high neurovirulence. In other words, HSV-1 rarely invades the CNS, but when it does, the consequences are almost always fatal.

All members of the family Herpesviridae are large enveloped double stranded DNA viruses and encode at least 30 different virion polypeptides (Roizman and Sears, 1996). Five of these proteins participate in viral entry. The herpesvirus glycoprotein C (gC) is the major glycoprotein responsible for virus attachment to cells (WuDunn and Spear, 1989; Figure 1). The glycosaminoglycan, heparan sulfate, serves as a receptor for gC. In the absence of gC, other herpes virus glycoproteins such as gB can mediate attachment to heparin sulfate. Viral attachment to heparan sulfate, however, is not sufficient to mediate infection. Viral entry depends upon four additional glycoproteins, named gB, gD, gH, and gL (Spear *et al*, 2000). In a series of elegant studies, several coreceptors for HSV-1 infection were identified. The first coreceptor identified was herpes virus entry mediator (HVEM) (Montgomery *et al*, 1996; Warner *et al*, 1998; Figure 1). This protein was found to belong to the TNF receptor family and has since been renamed herpes virus entry mediator A (HveA) or TNF receptor superfamily #14 (TNFRSF-14). Additional coreceptors were cloned that belonged to the immunoglobulin superfamily that included the poliovirus receptor or CD155, and two poliovirus receptor related molecules Prr2 and Prr1 (Cocchi *et al*, 1998; Geraghty *et al*, 1998; Warner *et al*, 1998; Figure 1). These later two proteins were renamed HveB, or Nectin 2α, and HveC or Nectin 1α. The nectins are a subfamily of adhesion molecules within the immunoglobulin superfamily of proteins. The herpes virus glycoprotein D (gD) interacts with all of these coreceptor proteins. In contrast to the ubiquitous distribution of heparan sulfate, these coreceptors are differentially expressed in different tissues and therefore play a major role in tropism. It is not clear which of these coreceptors predominates in CNS tissue.

Cellular receptors for rabies virus

Rabies virus belongs to the lyssavirus genus of the family Rhabdoviridae (for a recent review see (Plotkin, 2000). Following exposure to the rabies virus by the bite of an infected mammal, cell free virus gains access to the nervous system. Neurons at the neuromuscular junction are infected first,

and this is thought to be mediated by a specific interaction between the rabies virus glycoprotein G and acetylcholine receptors (Lentz *et al*, 1982; Gastka *et al*, 1996; Figure 1). The virus then travels by retrograde axonal transport to cell bodies. Replication in neurons leads to further spread of virus in the CNS. Rabies is also transported by anterograde axonal transport to the skin and salivary glands where it can be transmitted to new susceptible hosts. Other molecules that have been implicated as rabies virus receptors include the neural cell adhesion molecule (NCAM) and the low affinity nerve growth factor (NGF) receptor (Thoulouze *et al*, 1998; Tuffereau *et al*, 1998; Figure 1). Recently, fibronectin has been implicated as a receptor for viral hemorrhagic septicemia virus (VHSV), a salmonid rhabdovirus causing significant mortality in rainbow trout (Bearzotti *et al*, 1999). Whether fibronectin can serve as an alternative receptor for rabies in some tissues is not known.

Cellular receptors for JC virus (JCV)

JCV was originally isolated from the brain of a patient with progressive multifocal leukoencephalopathy (PML) and subsequently propagated in cultures of human fetal glial cells (Padgett *et al*, 1971). As these cells are difficult to obtain, virus isolation and propagation was attempted in a wide variety of other cell types with little or no success (Major *et al*, 1992). As a result of these early studies, JCV was characterized as having a very narrow host range. *In vivo*, JCV infection is restricted to oligodendrocytes, astrocytes, and B-lymphocytes (Houff *et al*, 1988; Monaco *et al*, 1996). This highly restricted cell type specificity is also seen it in vitro as virus infection is restricted to primary cultures of human glial cells and to a few established human glial cell lines.

JCV, like most other polyomaviruses, hemagglutinates red blood cells in a sialic acid dependent manner. Until recently, very little was known about JCV receptors on cells other than erythrocytes. The first suggestion that receptors played a role in tropism came from a comparison of the ability of JCV virions or JCV DNA to initiate early viral gene expression in nonpermissive HeLa cells. In these experiments, JCV virions did not infect HeLa cells and no early viral gene expression was detected (Schweighardt and Atwood, 2000). In contrast, transfection of JCV DNA into the HeLa cells led to early viral gene expression (Schweighardt and Atwood, 2000). This suggests that one block to infection of nonpermissive cells by JCV is at an early stage in the viral life cycle, perhaps at the level of receptor binding. The nature of the glial cells receptor for JCV was then characterized biochemically. These data demonstrated that infection of glial cells by JCV can be inhibited by treating cells with tunicamycin, or by enzymatic removal of α (2-3) and α (2-6) linked sialic acids (Liu *et al*, 1998). A recombinant α (2-3) specific neuraminidase did not inhibit infection of these cells by JCV suggesting that the α (2-6) linkage is critical. Infection of cells by JCV was also not inhibited by an O-linked glycosylation inhibitor, BenzylGalNac, or by trypsin, chymotrypsin, phospholipase A2, or phospholipase C. These data when taken together demonstrate that the JCV receptor is a trypsin resistant *N*-linked glycoprotein containing α (2-6) linked sialic acid (Liu *et al*, 1998; Figure 1). These properties distinguish JCV from other polyomaviruses that use sialic acid as cell surface receptors. It is interesting to note that treatment of glial cells with trypsin reduces virus binding to cells but, paradoxically, leads to increased infectivity (our unpublished observations). This may be due to the elimination of pseudoreceptors for JCV that act to limit accessibility to specific and productive receptor binding sites.

Recently, JCV binding to a wide variety of permissive and nonpermissive cells was studied by flow cytometry. JCV bound to all of the cell lines tested, regardless of their known susceptibility to infection (Wei *et al*, 2000). An α (2-6) linked sialic acid specific lectin, SNA, also bound to all of these cells. It is therefore likely that many cell surface glycolipids and glycoproteins are modified by α (2-6) sialyation but that only a minority of these molecules can serve as a specific receptor for JCV. Interestingly, when JCV binding to primary cells was examined, a different story emerged. In these experiments, JCV bound only to primary cells that were known to be susceptible to infection. For example, virus bound to primary human glial cells, to primary tonsillar stromal cells, and to primary human B cells but did not bind to primary human T cells (Wei *et al*, 2000). This indicates that there may be specificity of JCV binding *in vivo* that is not apparent when one examines virus binding to tumor cell lines. The identification of a specific glial cell receptor for JCV has remained elusive.

Cellular receptors for HIV-1

Human Immunodeficiency Virus (HIV)-associated dementia affects approximately 20% of HIV-infected individuals (Lipton, 1994; McArthur *et al*, 1997). It is characterized by progressive cognitive and motor dysfunction (Atwood *et al*, 1993; Kolson *et al*, 1998). The neuropathology of HIV dementia includes diffuse damage to white matter, loss of synaptic density, vacuolization of dendritic processes, reactive astrogliosis, and the appearance of multinucleated giant cells (Epstein and Gendelman, 1993; Everall *et al*, 1991; Kolson *et al*, 1998).

The presence of HIV within the central nervous system (CNS) is not sufficient to cause dementia. Proviral HIV DNA has been isolated from brain within 2 weeks of primary infection, providing evidence that HIV invades the CNS early during the course of infection (Davis *et al*, 1992). However, most HIV infected individuals do not develop HIV associated dementia until the terminal stages of AIDS when CD4 counts are at their lowest, suggesting that an intact immune system may protect the CNS from dementia (Brew *et al*,

1996; Soontornniyomkij *et al*, 1998). In addition, the incidence of HIV dementia is reduced in individuals receiving effective anti-retroviral therapy, suggesting that reducing systemic viral replication limits CNS damage (Brodt *et al*, 1997; Dore *et al*, 1999).

In the CNS, perivascular microglial cells and infiltrating macrophages are the predominant cell types productively infected by HIV (Gabuzda *et al*, 1986; Watkins *et al*, 1990; Jordan *et al*, 1991; Wiley *et al*, 1986). HIV proviral DNA as well as early and late viral gene products are readily detected within these cell types *in vivo* (Koenig *et al*, 1986; Wiley *et al*, 1986; An *et al*, 1999a). Infection of macrophages by HIV involves the cellular receptors CD4 and CCR5 (Alkhatib *et al*, 1996; Deng *et al*, 1996; Doranz *et al*, 1996). Initially, the viral envelope glycoprotein, gp120, binds to the cellular receptor CD4 (Figure 1). This interaction induces a conformational change within the gp120 molecule which exposes, or creates, a binding site for CCR5, the chemokine receptor that serves as the main coreceptor for macrophage tropic strains of HIV-1. (Kwong *et al*, 1998; Rizzuto *et al*, 1998; Wyatt *et al*, 1998; Figure 1). It has been determined that the tropism of different strains of HIV is determined by the coreceptor binding site of the viral gp120 (Chan and Kim, 1998; Littman, 1998; Rizzuto *et al*, 1998). Interaction of gp120 with the coreceptor induces further conformational changes within the envelope glycoproteins that expose a fusogenic domain in gp41, which consequently leads to the virus-cell fusion event. Microglia, which are also a CD4 positive cell-type, have been shown to be highly susceptible to infection by macrophage tropic strains of HIV (Watkins *et al*, 1990; Jordan *et al*, 1991). Microglia express the β-chemokine receptors, CCR5 and CCR3. HIV infection of microglial cells can be inhibited by pretreatment with the ligands of these two coreceptors, RANTES and eotaxin respectively, implying that both CCR3 and CCR5 play a role in HIV infection of microglia *in vivo* (He *et al*, 1997; Shieh *et al*, 1998).

Despite the fact that neuronal damage leads to the symptoms of dementia, there is little evidence of direct infection of neurons by HIV. This indicates that neurons are being damaged indirectly (Everall *et al*, 1991; Masliah *et al*, 1992; Gelbard *et al*, 1995; Bagasra *et al*, 1996; Nuovo and Alfieri, 1996; Brannagan *et al*, 1997). Infected macrophages are known to secrete many potentially neurotoxic substances, such as inflammatory cytokines, quinolinic acid, and nitric oxide (Dawson *et al*, 1993). It is likely that the presence of infected macrophages within the CNS contributes to the neuropathogenesis of HIV dementia (Lipton, 1994).

There is limited evidence to suggest that oligodendrocytes are directly infected by HIV. HIV DNA has been detected by in situ hybridization in cells that have the morphology of oligodendrocytes (Nuovo *et al*, 1994; Bagasra *et al*, 1996). More recently, HIV DNA was detected in oligodendroctyes *in vivo* using a more sensitive technique called polymerase chain reaction/*in situ* hybridization (PCR-IS) (An *et al*, 1999b). However, positive identification of oligodendrocytes in tissue sections can be difficult due to problematic staining for galactocylceramide (GalCer), the most commonly used oligodendrocyte marker (Albright *et al*, 1996). In many cases, researchers must rely on morphological characterization alone to identify oligodendrocytes. However, *in vitro* studies have demonstrated that purified adult oligodendrocytes in culture are able to support a restricted infection by some strains of HIV (Albright *et al*, 1996). The cellular receptors involved in HIV infection of oligodendrocytes have not been identified.

HIV has been found to establish a persistent infection in astrocytes *in vivo* and in culture (Conant *et al*, 1994; Nuovo *et al*, 1994; Tornatore *et al*, 1994a; Tornatore *et al*, 1994b; Nath *et al*, 1995; Ranki *et al*, 1995; Bagasra *et al*, 1996; An *et al*, 1999a; An *et al*, 1999b). Proviral DNA and early viral gene products are detected in astrocytes *in vivo*, however, late viral gene products are not detected (Nuovo *et al*, 1994; Ranki *et al*, 1995; Bagasra *et al*, 1996; An *et al*, 1999a; An *et al*, 1999b). In primary cultures of human fetal astrocytes, HIV establishes a low level, noncytopathic infection, which becomes latent after several days of virus production (Tornatore *et al*, 1994b; Tornatore *et al*, 1993; Tornatore *et al*, 1991) The latent infection in astrocytes can be reactivated by treatment of the cells with TNFα, IL-1β, and phorbol esters such as PMA (Tornatore *et al*, 1993). Astrocytes are often referred to as a reservoir of HIV within the CNS because they restrict viral replication, yet can still transfer infection to other susceptible cell types (Brack-Werner, 1999). Astrocytes also provide HIV with a sanctuary from antiviral therapy, because many of the current antiviral drugs do not efficiently cross the blood–brain barrier (Brack-Werner, 1999; Kerza-Kwiatecki and Amini, 1999). Persistently infected astrocytes may provide a continuous source of infectious virus *in vivo*, even within an individual whose systemic viral load has been dramatically reduced by anti-viral therapy (Kerza-Kwiatecki and Amini, 1999).

The CD4-independent mechanism by which HIV-1 enters astrocytes has not been defined. One group has reported that a 260kDa protein located on the surface of fetal astrocytes binds gp120, however, it remains to be determined whether or not this molecule can serve as a receptor for HIV-1 entry (Ma *et al*, 1994). Another group has reported that gp120 binds to a 65kDa molecule on the surface of human astrocytes, but again, its involvement in HIV entry has not been determined (Hao and Lyman, 1999). Astrocytes have been found to express several chemokine receptors, including CXCR2, CXCR4, CCR1, and CCR5 (Hesselgesser and Horuk, 1999). The role of chemokine receptors as HIV coreceptors suggests that these receptors may play a role in the entry of HIV into astrocytes. However, one group has found no involvement of major chemokine receptors in infection of astrocytes by HIV-1 (Sabri *et al*, 1999). This

is supported by our study demonstrating that neither CD4 nor CXCR4 are involved in infection of an astrocyte cell line by a T-tropic strain of HIV-1 (Schweighardt *et al*, 2001).

Conclusions

As our knowledge about cellular receptors for viruses grows it is becoming increasingly apparent that virus-host cell receptor interactions play a major role in determining viral tropism *in vivo*. The picture is complicated by the fact that many viruses are now being shown to require more than a single receptor to infect a cell. Moreover, tissue specific differences in receptor glycosylation also contribute significantly to virus tropism. As the complexities of these virus-host cell receptor interactions unfold, novel strategies to treat or prevent viral infection of the CNS should present themselves. In addition, increased knowledge about virus receptors may facilitate more accurate delivery of therapeutic genes to specific cell types to treat a variety of diseases. The development of small animal models based on the expression of receptor transgenes should facilitate the rapid discovery of receptor based therapeutics.

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