

## Molecular mechanisms of HIV-1 associated neurodegeneration

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Since identification of the human immunodeficiency virus-1 (HIV-1), numerous studies suggest a link between neurological impairments, in particular dementia, with acquired immunodeficiency syndrome (AIDS) with alarming occurrence worldwide. Approximately, 60% of HIV-infected people show some form of neurological impairment, and neuropathological changes are found in 90% of autopsied cases. Approximately 30% of untreated HIV-infected persons may develop dementia. The mechanisms behind these pathological changes are still not understood. Mounting data obtained by *in vivo* and *in vitro* experiments suggest that neuronal apoptosis is a major feature of HIV associated dementia (HAD), which can occur in the absence of direct infection of neurons. The major pathway of neuronal apoptosis occurs indirectly through release of neurotoxins by activated cells in the central nervous system (CNS) involving the induction of excitotoxicity and oxidative stress. In addition a direct mechanism induced by viral proteins in the pathogenesis of HAD may also play a role. This review focuses on the molecular mechanisms of HIV-associated dementia and possible therapeutic strategies.

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### 1. Introduction

Human immunodeficiency virus-1 (HIV-1), widely believed to be the causative agent of acquired immunodeficiency syndrome (AIDS), is the cause of a worldwide health crisis. According to the World Health Organization (WHO) and United Nations AIDS (UNAIDS), in 2004, the number of people living with HIV are totalled 39.4 million (35.9–44.3 million). Out of this number there are 37.2 million adults, of which 17.6 million are women. About 2.2 million children under the age of 15 years are also infected. In 2004, almost five million people became newly infected with HIV, the greatest number in any one year since the beginning of the epidemic. At the global level, the number of people living with HIV continues to grow – from 35 million in 2001 to 38 million in 2003. In 2004, more than three million were killed by AIDS. In total, over 20 million have died since the first

cases of AIDS were identified in 1981 (UNAIDS 2004). The HIV/AIDS pandemic continues to spread at an accelerated rate, 15000 new infections every day. Despite the reduction of new cases in industrialized countries due to early diagnosis and treatment opportunities and prevention programmes, the vast majority of new infections occur in developing countries such as India, China and underdeveloped countries in Asia and Africa. The combined population of India and China is more than one third of the world population. However, data from these two countries are insufficient to make proper assessment on the extent of the problem in those countries. For instance, an estimated 4 million Indians are infected with HIV. Subtype C is the major circulating HIV-1 strain in that region, although variation in this strain and non-C subtypes were also observed (Jameel *et al* 1995; Sehgal *et al* 1996; Gadkari *et al* 1998, Osmanov *et al* 2002). The high cost of anti viral treatment and lack of a comprehen-

**Keywords.** HIV-1; Neurodegeneration; Neuronal apoptosis

Abbreviations used: AIDS, Acquired immunodeficiency syndrome; BMVEC, brain microvascular endothelial cells; CNS, central nervous system; CSF, cerebrospinal fluid; FKN, fractalkine; HAART, highly active antiretroviral therapy; HAD, HIV associated dementia; LTR, long terminal repeat; PAF, platelet activating factor; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; ROS, reactive oxygen species; SIV, simian immunodeficiency virus.

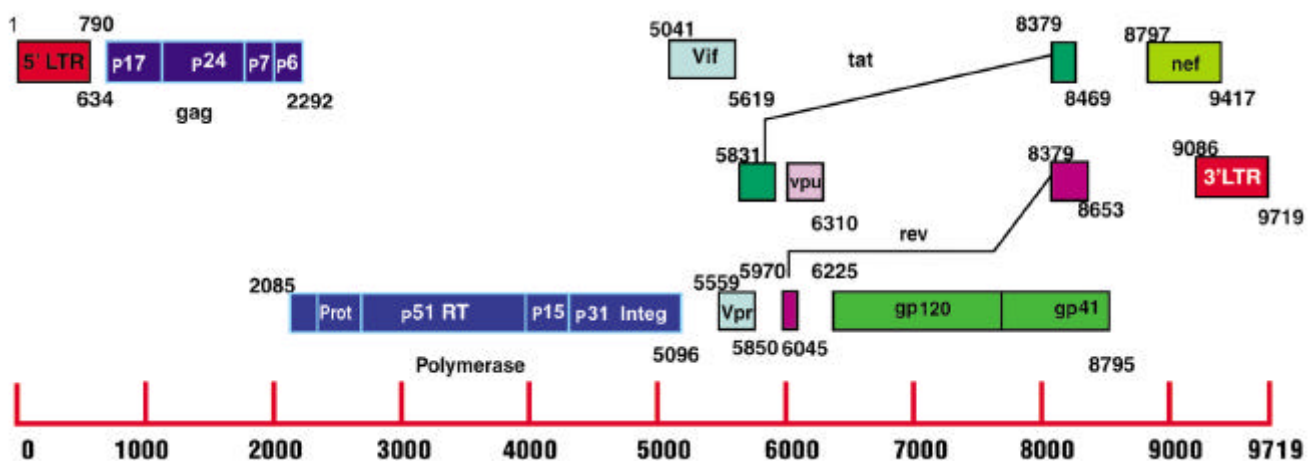
sive prevention program are still major obstacles to control/reduce HIV infection and therefore HIV-associated diseases including dementia. HIV-1 infection is a multi-system infection. Transmission of HIV is dependent on biological and behavioral factors (Holmberg *et al* 1989; Padian *et al* 1997). HIV is transmitted by sexual relations, breast feeding, contaminated blood products, contaminated needles, and through maternal-fetal circulation. Clinical features of HIV infection are dependent on the stage of HIV infection and vary from flu-like symptoms to extreme multi-system immunodeficiency symptoms and disease. HIV enters into the bloodstream directly and is delivered to lymphoid tissues, spleen, lung and liver (Cashion *et al* 1999). HIV-1 invades the central nervous system (CNS) at the early phase of infection and induces progressive multiple symptoms of motor, cognitive dysfunction and behavioural changes. Major clinical symptoms include forgetfulness coupled with difficulty in mental concentration, leg weakness, slowness of hand movements and gait as well as depression (Koutsilier *et al* 2001). The terms AIDS dementia complex (ADC) or HIV-1-associated dementia are used to describe these neurological and psychiatric symptoms caused by HIV infection (Janssen *et al* 1992; Reger *et al* 2002). HIV-1-associated dementia affects 15–20% of the patients in the late stages of AIDS. HIV-1-induced neuropathology can be identified at autopsy in over 90% of cases. In the United States, HIV-1 infection is the most common cause of dementia in young adults (Janssen 1992; McArthur *et al* 1999).

## 2. Biology of HIV-1 and cellular tropism

HIV-1 was the third human retrovirus discovered after the adult T cell leukemia-associated viruses (HTLV-I and

HTLV-II) (Barre-Sinoussi *et al* 1983; Gallo *et al* 1984). HIV-1 is an enveloped animal RNA virus with two positive strands, which is classified as a lentivirus within the retroviridae family. The HIV-1 genome is over 9200 base pairs long (Muesing *et al* 1985; Wain-Hobson *et al* 1985). The typical HIV genome includes the long terminal repeat (LTR) at both ends and has three major coding regions, which encode core (gag), polymerase (pol) and envelope (env) gene products (figure 1). The HIV genome also encodes several 'accessory' proteins such as Nef, Tat, Vpr, Vif, Rev and Vpu that may play a key role in the pathogenesis of HIV infection (Frankel and Young 1998). HIV-1 replication is regulated by complex interactions between cellular transcription factors and the viral trans-activators. The HIV-1 LTR is critically important for efficient virus replication within cells of the monocyte lineage. Studies indicate that LTR may have a role in promoting the establishment of an HIV latent infection (Burdo 2004; Nonnemacher *et al* 2004).

CD4+T cells and macrophages are major targets for HIV infection (Kedzierska and Crowe 2002). HIV-1 infects CD4+T cells by utilizing CD4 as a receptor. It has been shown that HIV also needs certain chemokine receptors as co-receptors (Philpott 2003). The criteria for cellular tropism can be defined in terms of the ability of HIV to grow in cells *in vitro*. HIV isolates that can infect and grow productively in macrophages and PBMC but less efficiently in T cell lines are called macrophage or M tropic. Whereas HIV isolates that can grow productively in T cell lines and PBMC but not in macrophages are classified as T tropic (Kedzierska and Crowe 2002). HIV isolates that can grow both in T and macrophage cells are called dual tropic (figure 2). Most of M tropic viruses utilize the CCR5 chemokine receptor, whereas most T-



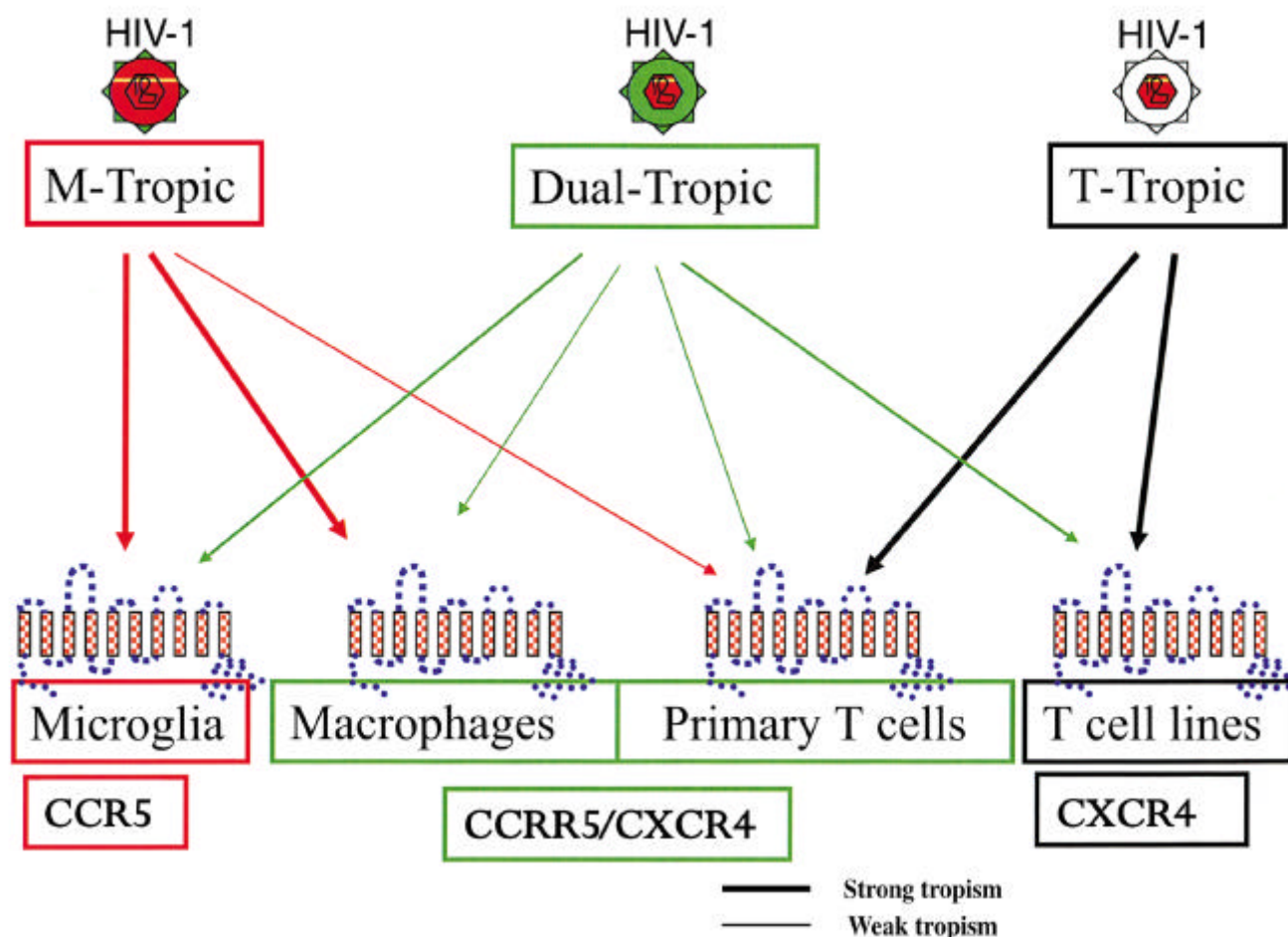
**Figure 1.** Representative genomic model of HIV-1 subtype HX-B2. HIV-1 genome is approximately 9.8 kilo bases in length and encodes 14 proteins, which may play different roles in promoting viral infection and virulence. Model was adapted from: [hiv-web.lanl.gov/content/immunology/pdf/2000/intro/GenomeMaps.pdf](http://hiv-web.lanl.gov/content/immunology/pdf/2000/intro/GenomeMaps.pdf)

tropic strains utilize CXCR4 chemokine receptors (Albright *et al* 1999). HIV strains and cellular tropism may play a role in HIV associated dementia (HAD) (Gorry *et al* 2002). The viral determinant of cellular and neurotropism is the gp120 envelope protein. In particular, the V3 region of gp120 is the major co-determinant for co-receptor use. Nucleotide changes in the HIV sequence are distributed throughout the genome. However, the change in V3 region is crucial for determination of HIV binding and entry (Liu *et al* 1990; Korber *et al* 1994; Westervelt *et al* 1991).

### 3. Pathological findings of HAD

Neurodegeneration is one of the characteristics of AIDS and is associated with neuronal apoptosis, brain atrophy and blood-derived monocyte infiltration into the brain

(Budka 1991; Everall *et al* 1991; Wiley *et al* 1991; Petit and Roberts 1995; Kaul *et al* 2001; Chen *et al* 2003). HIV-associated neurodegeneration is clinically manifested after many years of seroconversion. The presence of HIV-specific antibody and cytotoxic T cells in the cerebrospinal fluid (CSF) indicates that the brain may be susceptible to immune-mediated HIV clearance (Van Wielink *et al* 1990; Jassoy *et al* 1992). Elevated viral RNA in the plasma and viral load in CSF accompanied by low levels of CD4+ T cells are all indicators of greater risk in developing HAD (Foudraine *et al* 1998; Stankoff *et al* 1999). However, presence of HIV RNA in CSF does not correlated with HIV expression within brain parenchyma (Donaldson *et al* 1994; Sinclair *et al* 1994). Decline of peripheral CD4+ T cells usually occurs in late stage of HIV infection. In this stage, HIV infected macrophages become active and initiates secretion of viral proteins and trigger inflammatory cascade within the brain



**Figure 2.** A schematic diagram for HIV-1 cellular tropism. CD4 and chemokine receptors are required for HIV-1 infection. Macrophage-tropic HIV-1 strains utilize CCR5 and infect primary macrophages and primary lymphocytes which express both CD4 and CCR5 or CXCR4 on their surface. T cell-tropic HIV-1 strains infect primary lymphocytes and T cell lines via CXCR4 but not macrophage. Dual-tropic strains infect all 4 cell types via either CCR5 and CXCR4.

parenchyma resulting in neuronal destruction (Zink *et al* 1999).

Neuronal apoptosis is a common feature of HAD in the brains of adults and pediatric patients with HIV infection. Unlike other encephalopathies, HAD occurs without direct infection of neurons (Shi *et al* 1996; Corasaniti *et al* 2001). Cortical neuronal loss has often been described post-mortem in the brain of patients with AIDS (Everall *et al* 1991). Typical pathological changes in patients with HAD are multinucleated giant cells (HIV-1 envelope mediated fusion of microglia or macrophages), diffuse white matter pallor, reactive gliosis and cerebral atrophy. The mechanism of multinucleated giant cells formation is not well known, but the binding of HIV envelope protein to CD4+ cells may be involved in inducing this formation (Shieh *et al* 2000).

#### 4. Viral entry into the CNS and development of cellular injury

The mechanism of how HIV-1 enters into the CNS remains unclear. It is generally accepted that HIV enters the CNS shortly after systemic infection via infiltration of infected CD4+ monocytes and perivascular macrophages (Trojan Horse hypothesis) (Peluso *et al* 1985; Glass *et al* 1995; Liu *et al* 2000). The relative numbers of these infected cells are low, although they serve as a reservoir of HIV. Productive HIV infection has been shown in microglia, macrophages, and multinucleated giant cells in the CNS but not in neurons, oligodendrocytes and astrocytes (Dewhurst *et al* 1996). Productive infection of HIV requires complex interaction between viral and host cell factors. Despite expression of chemokine receptors on neurons, expression of CD4+ receptors is not found on neurons. Astrocytes are the most numerous cell type in the brain, and their physiological roles are essential for normal brain function. Infection of HIV in astrocytes is different from productive infection of HIV in microglia (Gartner and Liu 2002). Astrocyte infection by HIV-1 *in vivo* is generally non-productive and can only be readily detected by sensitive techniques that detect HIV-1 RNA or proviral DNA (Trillo-Pazos *et al* 2003). Astrocytic cell lines can be permissive to infection by HIV-1 strains but are refractory to efficient HIV-1 expression. Infection of astrocytes is restricted by post entry since early transcription products were detected (Kanmogne *et al* 2002; Galey *et al* 2003; Gorry 2003; Kim *et al* 2003; Su *et al* 2003). In contrast to HIV infection in microglia, which produces viral genomic RNA upon stimulation, astrocytes produce only multi-spliced RNA even after stimulation (Tornatore *et al* 1994). One recent study indicated that HIV-1 expression in astrocytes profoundly alters host cell biology by increasing transcription of 266 genes and suppressing

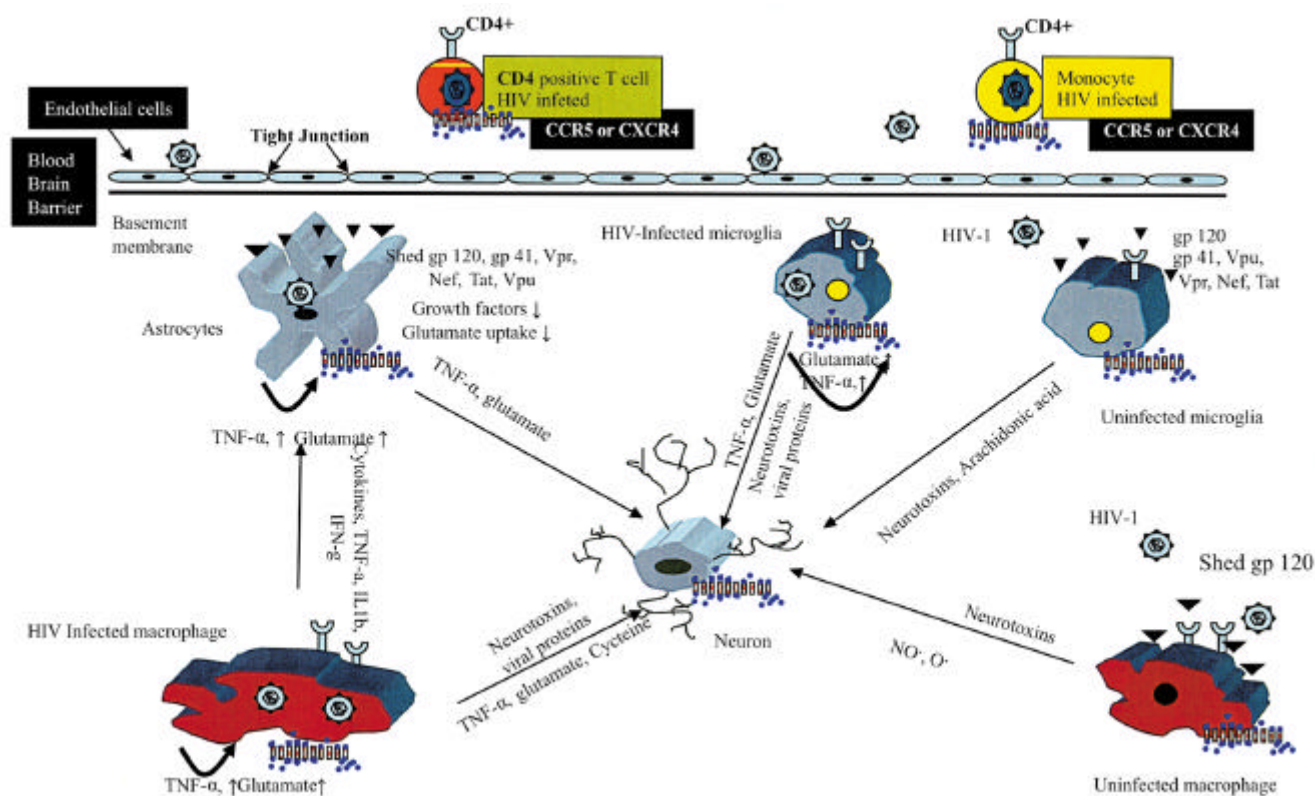
expression of 468 (Wang Z *et al* 2004). Another study showed that viral protein Tat expression resulted in a significant increase in glial fibrillary acidic protein (GFAP, indication of astrocytosis) expression in astrocyte at the transcriptional level (Zhou *et al* 2004). A recent study indicated that the V3 region of the HIV envelope gene amplified from pure astrocytes, neighbouring macrophages and multinucleated giant cells obtained from the brain tissue of patients who died with HIV-associated dementia has a distinct sequence (Thompson *et al* 2004). In the future, a better understanding of the mechanism of HIV-1 infection in astrocytes may help us to design novel strategies to suppress/restrict viral replication in CD4+ cells. HIV can also infect choroid plexus and blood brain barrier epithelial cells (Harouse *et al* 1989; Kanmogne *et al* 2002; Falangola *et al* 1995; Mukhtar and Pomerantz 2000). HIV DNA obtained from the brain or spleen of infected persons grouped into two distinct clusters, while DNA sequence from the choroids plexus contained viral strains that were a mixture of those found in the brain or spleen. This result indicates that the choroid plexus may be a site where HIV-1 gains access to the brain from the blood. Therefore, choroids plexus contains viruses that are of both genotypes and it may serve as a reservoir for HIV infection (Petito 1999; Chen *et al* 2000). Choroid plexus infection has been shown in experimental simian immunodeficiency virus (SIV) and feline immunodeficiency virus infection (FIV) (Lackner *et al* 1991; Bragg *et al* 2002).

Chemokines have highly diverse mechanisms of action and cellular targets in the CNS. Chemokine receptors have important roles in the pathogenesis of HIV infection, since they are utilized as co-receptors for HIV entry (figure 2). There are more than a dozen chemokine receptors involved in HIV pathogenesis, however, three of them CXCR4, CCR5 and CCR3, are crucial for viral adhesion and entry into the target cells. HIV infections utilizing CXCR4 was found to be more cytopathic compared to those using CCR5 and CCR3. The envelope region of HIV may have a major role in this process (Ohagen *et al* 1999).

The presence of chemokine receptors on neurons suggests that chemokines may have roles in the development of HAD (Klein *et al* 1999; Miller and Meucci 1999; Zheng *et al* 1999). A growing body of evidence suggests that the role of chemokines in the pathogenesis of HAD is not limited to virus entry but chemokine receptor signalling may also be involved in modulating neuronal apoptosis and neurotoxicity via induction of glutamate release and through a G-protein-mediated modulation of L- and N-type calcium channels (Allen and Attwell 2001; Bezzi *et al* 2001; Giovannelli *et al* 1998). Additionally, some chemokines are suppressive factors for HIV-1 infection. Antagonists of CXCR4 and CCR5 may inhibit HIV entry (Cocchi *et al* 1995; Bleul *et al* 1996; Oberlin

*et al* 1996). In particular, CXCR4 and its ligand, SDF-1, may play a crucial role in the inhibition of gp120 induced neuroapoptosis, indicating that CXCR4 signalling plays a role in HIV-induced dementia (Biard-Piechaczyk *et al* 2000; Bezzi *et al* 2001; Corasaniti *et al* 2001). Another important chemokine receptor, CX3CR1, and its ligand, fractalkine (FKN) is expressed on the cell surface of microglia, neuron and macrophages (Maciejewski-Lenoir *et al* 1999; Meucci *et al* 2000). FKN is suggested to play an important role in inflammatory brain diseases because of its chemotactic properties. Increased levels of CX3CR1 and FKN have been shown in pediatric patients with HIV-encephalitis (Tong *et al* 2000). Intrathecal FKN release was observed in the majority of patients with HIV infection. Increased FKN levels were detected in CSF samples of patients with HIV-induced CNS disorders compared to infected patients without cognitive impairment. These results suggest a dysregulation of brain soluble FKN release during HIV infection (Cotter *et al* 2002; Erichsen *et al* 2003; Sporer *et al* 2003). In microglia and neurons, FKN signalling increases intracellular  $Ca^{2+}$  and induces Akt and ERK 1–2 kinase activation suggesting that FKN may induce neuroprotection (Meucci *et al* 1998).

Neuronal apoptosis in HAD might be caused by indirect effects of released neurotoxins and neuromodulators from activated astrocytes and microglia, or by direct effects of HIV proteins such gp120, gp41, Vpr, Tat, Nef, Vpu on neurons or a combination of both (figure 3). Among shed viral proteins from infected cells, gp120 has been shown in the CSF and in the brain of patients with HIV encephalitis and dementia (Buzy *et al* 1992; Jones *et al* 2000; Van de Bovenkamp *et al* 2002). The direct effects of the neurotoxic potential of gp120 have been studied in detail, in the absence of other contaminating cell types, using different types of neurons such as rodent cortical, hippocampal and retinal ganglion neurons (Dreyer *et al* 1990; Lipton *et al* 1991; Dawson *et al* 1993; Corasaniti *et al* 1998; Catani *et al* 2000). Studies have indicated that HIV envelope protein and other viral proteins shed by infected cells may change intracellular signalling and can induce apoptosis (Yeung *et al* 1995; Scorziello *et al* 1998; Catani *et al* 2000; Bonavia *et al* 2001). The exact mechanism by which these proteins cause neuronal damage is unknown. It has been shown that the glutamate-mediated cell death caused by gp120 proceeded through the recruitment of  $Ca^{2+}$ -dependent enzymes such as nitric



**Figure 3.** Schematic representative model for potential interaction between HIV-1 infection and cells of the CNS involving cellular signalling and crosstalk between glial cells. Activated microglia produce chemokines, proteases, excitotoxins, and cytokines that activate other glial cells which may cause neuronal damage.

oxide synthase and calpain along with membrane lipid peroxidation (Corasaniti *et al* 1995, 1996; Nagano *et al* 2001). HIV gp120 increases cytoplasmic  $\text{Ca}^{2+}$  in two ways: facilitating glutamate neurotransmission with subsequent increase of  $\text{Ca}^{2+}$  conductance and activating the IP3 pathway, which facilitates  $\text{Ca}^{2+}$  release from the smooth endoplasmic reticulum (Scorziello *et al* 1998; Galicia *et al* 2002). Recently, it was shown that injection of gp120 induces neuronal apoptosis which can be prevented by inhibition of TNF- $\alpha$  and CXCR4 signalling (Kaul and Lipton 1999). TNF- $\alpha$  may modulate neuronal apoptosis by increasing voltage dependent calcium currents (Soliven and Albert 1992; Yu *et al* 2000). The ability of gp120 to induce apoptosis is regulated by activation of CXCR4 followed by p38 mitogen activated protein kinase downstream signalling, activation of caspase 3 and enhancement of Bax expression (Ullrich *et al* 2000; Biard-Piechaczyk *et al* 2000). Other evidence of gp120 induced neuronal apoptosis is that transgenic mice expressing gp120, without productive infection, show microglial activation, astrogliosis, altered expression of immunoproteins and increased blood brain barrier permeability (Banks *et al* 1997; Cioni and Annunziata 2002).

HIV-1 vpr is a regulatory protein that is required for effective infection. Vpr is also detected in the CSF of patients with HAD. It was shown that HIV-1 Vpr can induce cell cycle arrest followed by neuronal apoptosis in both human and Ntera2 neurons as measured by increasing activation of caspase 8 (Patel *et al* 2000; Stewart *et al* 2000).

So far, it is generally accepted that HIV infection in the CNS can cause neuropathological changes through indirect effects of infected cells on neurons (Glass and Johnson 1996) (figure 3). Indirect evidence of neuronal apoptosis triggered by gp120 *in vitro* seems to be related to the induced secretion of neurotoxic factors, such as cytokines, eicosanoids, excitotoxins and free radicals (Kaul *et al* 2001). After infection of brain cells by HIV, secretion of neurotoxins from infected cells may cause multicellular complex interactions between the CNS cells. It has been shown that neurotoxins secreted from HIV infected cells can cause metabolic alterations in CNS cells (Giulian *et al* 1993). Most of the apoptotic cells found in the CNS are not HIV infected cells but surrounding cells, suggesting that soluble factors may be involved. Proinflammatory cytokines secreted from infected or activated cells may directly induce cell death (Pulliam *et al* 1994).

### 5. Possible mechanisms of cellular death and roles of microglia and astrocytes

Reactive astrogliosis and microgliosis is another major characteristics of HAD (Kaul *et al* 2001; Garden 2002; Ghorpade *et al* 2003). Astrocytes may be involved in the

etiology of HAD, serving as a reservoir for non-productive HIV-infection and they may have preventive roles against neurotoxins secreted by HIV-infected and activated microglia. The significantly lowered levels of proinflammatory molecules in co-cultures of activated macrophages and astrocytes compared to cultures of macrophages alone indicate that astrocytes may have a protective role (Tornatore *et al* 1994; Nottet *et al* 1995; Hori *et al* 1999). Other studies indicated that HIV-1 Tat and gp120 expression also markedly impaired glutamate uptake by astrocytes as shown by transcriptional inhibition of the EAAT2 glutamate transporter gene, and cell culture supernatants from Tat-expressing astrocytes inducing neuronal death (Zhou *et al* 2004; Wang *et al* 2004).

HIV-infected macrophages/microglia are capable of producing viral proteins such as gp120, Tat, Nef, Vpr. These secreted viral proteins have been shown to possess neurotoxic and/or neuromodulatory features *in vitro*. In addition, microglia and macrophages activated by HIV-1 gp120 appear to secrete excitants/neurotoxins such as arachidonic acid, platelet-activating factor, free radicals ( $\text{NO}^{\bullet}$  and  $\text{O}_2^{\bullet-}$ ), glutamate, quinolinate, cysteine, cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), chemokines, amines, and as yet unidentified factors that may play a role to reactive astrocytes (Lipton 1996; Van de Bovenkamp *et al* 2002; Eugenin *et al* 2003). Elevated serum levels of proinflammatory cytokines (TNF, IFN- $\gamma$ , IL-1 $\beta$ , arachidonic acid), inducible nitric oxide synthase, quinolate, PAF, glutamate and quinolinic acid in cerebrospinal fluid have been shown to have a high correlation with HIV-dementia (Griffin *et al* 1994; Yeung *et al* 1995; Gendelman *et al* 1998; Schulz *et al* 2000; Jiang *et al* 2001; Smith *et al* 2001; Vecchiet *et al* 2003). Another study showed that reduced N-acetylaspartate levels have been demonstrated by proton magnetic resonance spectroscopy (MRS) would be used to monitor HIV infection and its neurological impairments (McConnell *et al* 1994). Increased levels of prostaglandin  $\text{E}_2$  ( $\text{PGE}_2$ ) in the cerebrospinal fluid of patients with HAD suggests that  $\text{PGE}_2$  may play a role in progression of dementia (Griffin *et al* 1994).

Studies reported that cellular factors secreted by microglia and macrophages as well as viral proteins such gp120, Vpr, and Tat promote neuronal toxicity via the NMDA type glutamate receptor (Doble 1999; Nishida *et al* 1996). Activation of the NMDA receptor may initiate caspase activation or promote calcium influx. This effect could be blocked with NMDA receptor antagonists. Platelet activating factor (PAF) released from cultured microglia in response to TNF stimulation can induce neuronal apoptosis via Bcl-2 independent pathways (Westmoreland *et al* 1996; Perry *et al* 1998). Elevated PAF also induces  $\text{Ca}^{2+}$  influx, arachidonic acid release and chemotaxis (Westmoreland *et al* 1996; Del Sorbo *et al* 1999).

Activated microglia in patients with HAD display increased expression of TNF- $\alpha$ , TNFR, IL-1 $\beta$  and IL-1 $\beta$  converting enzyme (caspase 1) (Sippy *et al* 1995; Zhao *et al* 2001). Oxidative stress also has a role in neuronal apoptosis in patients with dementia (Toborek *et al* 2003; Turchan *et al* 2003). Nitric oxide synthase, arachidonic acid and P450 enzymes are sources of reactive oxygen species (ROS) in the brain and increased expression of inducible NOS correlated with expression of gp41 (Adamson *et al* 1999; Zhao *et al* 2001). Post mortem studies from pediatric patients with HIV indicate that caspase 3 expression caused by reactive oxygen intermediates was produced in mitochondria, although this activation was independent from Bcl2/Bax pathways (Banki *et al* 1998; James *et al* 1999). It has been shown that increased expression of Bcl-2 protects cells from HIV induced apoptosis (Doble 1990; Strack *et al* 1996).

Additionally, increased production of mitochondrial ROS led to caspase 8 activation in patients with HAD (Banki *et al* 1998; Accomero *et al* 1998). HIV-1 infected monocytes may induce cell adhesion molecules E-selectin and vascular cell adhesion molecules (VCAM-1) on the brain microvascular endothelial cells (BMVEC). Studies showed that secretion of TNF and IL-1 $\beta$  from HIV infected brains induced expression of adhesion molecules on BMVECs. These cell adhesion molecules are known mediators for transendothelial migration of monocytes (Scorziello *et al* 1998; Nottet *et al* 1996).

A number of studies indicate that patients with HAD have many clinical signs in common with dopaminergic disorders (Nath 1999; Czub *et al* 2001; Koutsilier *et al* 2001). Autopsy studies of patients with HAD indicate that HIV infected cells, including macrophages and multinucleated giant cells, are found infiltrating the dopamine rich basal ganglia (Navia *et al* 1986; Koutsilier *et al* 2001). It has been shown that the biogenic amine metabolite, homovanillic acid (HVA) and dopamine transporter levels are more diminished in patients with HAD compared to the patients with AIDS without neurological symptoms (Kramer and Sanger 1990; Berger *et al* 1994; Wang G J *et al* 2004). Dopamine deficits were found in association with a decrease in intracellular concentrations of cAMP and cAMP response element binding protein (CREB) in the brain of SIV infected monkeys (Jenuwein *et al* 2004). To try to explain how neurological symptoms develop, a limited number of studies also indicate that cholinergic systems may be involved in the pathogenesis of HAD (Koutsilier *et al* 2000). Overall, results indicate that dopaminergic systems may be involved in the pathogenesis of HAD.

## 6. Therapeutic strategies and HIV vaccine studies

The proteolytic cleavage of HIV polyproteins, pol and gag, is carried out by viral proteases required for virus

replication. Using this basic information, inhibitors against HIV-1 viral enzymes were designed and synthesized. The first HIV protease inhibitor, saquinavir (invirase) was received regulatory approval in 1995. Since then, many protease inhibitors have been approved (Dewhurst *et al* 2000). Protease inhibitors are typically used in combination with nucleoside reverse transcriptase inhibitors (AZT, 3TC) or non nucleoside reverse transcriptase inhibitors (viramune) for treatment of HIV infection. This combination of therapeutics is usually called a highly active antiretroviral therapy (HAART). Introduction of HAART has decreased mortality rates and the development of dementia. HAART has played a major role in improving the quality of life and cognitive functions for individuals with HIV infection (Suarez *et al* 2001; Sacktor 2002). HAART has also dramatically decreased the incidence of opportunistic infections and malignancies but did not eliminate new forms of HIV encephalitis and HIV leukoencephalopathy suggesting that direct cytopathic effects of neuronal tissue and the interactions of antiretrovirals with cerebrovascular endothelium, astroglial cells and white matter of the brain may lead to cerebral ischemia, increased blood-brain barrier permeability and demyelination followed by trophic factor dysregulation and mitochondrial injury (Gray *et al* 2003; Langford *et al* 2003; Moroni and Antinori 2003; Sperber and Shao 2003; Brew 2004). Following successful HAART, a prompt and early rise in CD4+ T cells was observed (Fleury *et al* 1998). It usually takes more than 2 years for pathological changes in the lymph nodes to return to normal after following HAART (Zhang *et al* 1999). However, extended survival of infected people leaves them more vulnerable to drug resistant neurological impairment and development of dementia (Czub *et al* 2001; Sperber and Shao 2003). With the increasing resistance of HIV strains to antiretrovirals there has been a resurgence in the frequency of HIV encephalitis and HIV leukoencephalopathy (Koutsilier *et al* 2001). Other limitations observed with HAART are that most of the drugs used in combinations with HAART have a very limited ability to penetrate into the CNS. With prolonged survival, HIV-infected patients are more susceptible to exposure to HIV virions and proteins because cells in the CNS may serve as a reservoir for HIV-1, protected from the impact of HAART. The compartmentalization of HIV-1 infection in the CNS may affect the treatment response, which may cause an evolution of viral drug resistance in the different compartments (Antinori *et al* 2003). These drugs became less effective in reducing viral load and eliminating higher replication rates of HIV in the CNS in many cases (Enting *et al* 1998; Cunningham *et al* 2000; Farinpour *et al* 2003). Minor cognitive motor disorders are now a more common neurological problem since HAART was introduced (Gray *et al* 2003; Bell 2004). The prevalence of sensory neu-

ropathies in patients with HAD receiving prolonged HAART is on the rise (McArthur 2004). Also increased use of protease inhibitors has revealed number of side effects on lipid metabolism and its storage (Carr *et al* 1998, 1999). Additionally, the cost of HAART is still a major obstacle for the treatment of HAD.

Since the introduction of the first anti-HIV drug, a number of novel antiviral drugs have been developed, including HIV-1 integrase inhibitor (Deng *et al* 1996; Anthony 2004). Another therapeutic drug developed was against the HIV-1 nucleocapsid protein zinc finger, which is involved in viral genome packaging and virus assembly (Druillennec *et al* 1999; Turpin *et al* 1999). Another successful approach has been to block virus entry and fusion using synthetic peptides (known as T-20, and D peptides, PRO 542), corresponding to a region of the HIV envelope gp41 protein (Jiang *et al* 1993; Kilby *et al* 1998; Cooley and Lewin 2003). Viral adsorption through binding to viral glycoprotein gp120 by synthetic molecules such polysulfates, polysulfones and polynucleotides is another experimental therapeutic approach considered for chemotherapeutic intervention (De Clercq 2003).

Immune modulators have also tried as an adjunctive approach to anti viral therapy. Although preliminary results are disappointing, inhibition of specific inflammatory mediators, such TNF- $\alpha$ , by specifically designed drugs in HIV-1 infected individuals has been investigated (Dezube *et al* 1997; Heijligenberg *et al* 1998). However, the use of interleukin-2 (IL-2) treatment helped to restore immune function in HIV infected persons by significantly increasing the number of CD4+ T cell in circulation (Levine *et al* 1996).

Other antiviral approaches are the use of immunostimulating or cyto-reductive strategies which force the latent HIV-1 reservoir in to the productive state or reduce the size of latent reservoir (Chun *et al* 1999; Smith *et al* 1998).

Based on increased knowledge of the pathogenesis of HAD, several potential experimental therapeutics, approaches to reduce CNS damage are under trial. The L-type voltage dependent  $Ca^{2+}$  channel antagonist, nimodipine, was one of the promising therapeutics. This drug binds to a particular class of calcium channels, inhibiting the cellular depolarization that occurs when extracellular glutamate concentrations are increased. However, the results from the nimodipine trials were controversial (Navia *et al* 1998; Pantoni *et al* 2000).

Another promising potential therapeutic agent is memantine, which is a low-to-moderate-affinity non-competitive NMDA receptor antagonist that inhibits the pathological results of NMDA receptor activation. Memantine has been investigated extensively in animal studies and subsequently, its efficacy and safety has been established and confirmed by clinical experience in humans with

dementia caused by neurodegenerative disorders, particularly Alzheimer's disease. It is available in the European Union and has recently been approved for moderate to severe dementia in the United States of America. *In vivo* and *in vitro* studies indicate that Memantine completely prevents neurotoxicity induced by HIV-1 viral proteins Tat and gp120 (Toggas 1996; Holden *et al* 1999; Jain 2000; Nath *et al* 2000; Anderson *et al* 2004; Sonkusare *et al* 2005). It has also been shown that nitroglycerin has protective effects against over stimulation of NMDA receptors (Lipton 1996). The mechanism of activation for nitroglycerin is similar to memantine preventing NMDA receptor over stimulation of neurons (Jain 2000).

Additionally, some chemokines are important potential therapeutic targets in the fight against HIV infection. Antagonists of CXCR4 and CCR5 may inhibit HIV entry (Cocchi *et al* 1995; Bleul *et al* 1996; Oberlin *et al* 1996). In particular, CXCR4 and its ligand, SDF-1 may play a crucial role in the inhibition of gp120 induced neuroapoptosis. Chemokine receptor, CX3CR1, and its ligand, FKN have been used to protect neurons from gp120-induced apoptosis.

There is also growing evidence that the brain of HIV-1 infected patients is in oxidative stress. This effect causes depletion of endogenous antioxidants and increases production of ROS. Consequently, antioxidant therapy may help to prevent the development of neurocognitive symptoms and neuronal apoptosis in the CNS (Shor-Posner *et al* 2002; Turchan *et al* 2003). Studies indicate that antioxidants (selegiline, CPI-1189, selenium) may help to reduce the incidence of development of cognitive symptoms in patients with AIDS (Bjugstad *et al* 1998; Sactor *et al* 2000; Koutsilieri *et al* 2001; Mollace *et al* 2001; Shor-Posner *et al* 2002). Finally, p38 MAPK inhibitors have been shown to reduce neuronal apoptosis (Bhat *et al* 1998; Ghatan *et al* 2000).

Since the first retrovirus therapy was successfully introduced, more than 40 different vaccine approaches against HIV infection have been explored world wide (Dewhurst *et al* 2000). Vaccines generated against recombinant HIV-1 gp120 proteins are the most well studied among other vaccine studies such nucleic acid vaccines (Boyer *et al* 1997; MacGregor *et al* 1998; Richmond *et al* 1998), multivalent vaccines (Caver 1999; Hanke *et al* 1999), plant based vaccines (Yusibov *et al* 1997), live attenuated vaccines (Baba *et al* 1999; Wyand *et al* 1999), and whole killed HIV vaccines (Richieri *et al* 1998).

## 7. Summary and future directions

Advances in research on HIV have included a better understanding of the molecular mechanisms of HAD. Although, neuronal apoptosis is essentially an irreversible process, it has been shown that HAART improves cogni-

tive functions, indicating that virus-induced neurological changes can be reversed. It is important to know when neurological damage becomes irreversible. Latency of HIV in the CNS cells is another important consideration for researchers. Understanding the activation and reactivation of HIV in the CNS will provide new insights into the development of effective therapeutic agents. Ultimately, studies on HIV and the pathogenesis of HAD will improve the quality of life and the life expectancy of patients with HIV and reduce the many complications of HIV infection.

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