HIV associated neurocognitive disorders

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Abstract

Human immunodeficiency virus type 1 is associated with the development of neurocognitive disorders in many infected individuals, including a broad spectrum of motor impairments and cognitive deficits. Despite extensive research, the pathogenesis of HIV-associated neurocognitive disorders (HAND) is still not clear. This review provides a comprehensive view of HAND, including HIV neuroinvasion, HAND diagnosis and different level of disturbances, influence of highly-active antiretroviral therapy to HIV-associated dementia (HAD), possible pathogenesis of HAD, etc. Together, this review will give a thorough and clear understanding of HAND, especially HAD, which will be vital for future research, diagnosis and treatment.

HIV neurobiology and neuroinvasion

Human immunodeficiency virus (HIV) is a member of the genus Lentivirus, part of the family of *Retroviridae*.[1] As is well known, HIV-1 is highly virulent and infective,[2] and is responsible for the current AIDS pandemic.[3] The HIV-1 genome contains three structural genes (*gag*, *pol* and *env*),[4] two regulatory genes (*tat* and *rev*) and four accessory genes (*nef*, *vif*, *vpr* and *vpu*). The HIV-1 genome also consists of at least seven structural elements (LTR, TAR, RRE, PE, SLIP, CRS, and INS).

The initial step of HIV infection is binding of the virions to the CD4 receptor and an additional co-receptor on the cell surface. Twelve chemokine receptors have been recognized acting as HIV co-receptors in cultured cells, but only two appear to play a more definitive role *in vivo*, CCR5 and CXCR4.[5] CCR5 can bind macrophage-tropic, non-syncytium-inducing (R5) viruses and it has been suggested to play a more pivotal role in the initiation and spread of HIV infection. This is based on the fact that R5 viruses are predominant not only during the early stages of HIV infection,[6] but more than half of HIV-infected individuals uniquely carry CCR5-using HIV strains throughout the course of their infection. Moreover, Individuals homozygous for *CCR5-Δ32* mutation, which is a 32bp deletion in the host *CCR5* gene, were described to be resistant to HIV infection by R5 strains,[7,8] although recent reports based on a single patient suggest that subsequent infection in patients harbouring *CCR5-Δ32* can occur via CXCR4 receptor.[9] Overall, the CCR5 or macrophage-tropic strains play a crucial role in HIV infection of the central nervous system (CNS).

Possible mechanism of HIV-1 entry into the central nervous system

The R5 viruses are the most common HIV-1 strains isolated from HIV-infected brains,[10] which has been reported as the second most frequently infected organ in HIV-infected individuals at autopsy.[11] HIV-1 entry into the brain at early phase of the infection can occur by several means,[12] including transcytosis; transition by infected endothelial cells, passage through the blood-cerebral spinal fluid (CSF) barrier of the choroid plexus (CPx),[13,14] and the *Trojan horse* model.[15,16] Transcytosis pathway is that where brain microvascular endothelial cells (BMVECs) take up HIV-1 particles into vacuoles from the blood side and release them on the brain side of the BMVECs. However, it is estimated that only less than 1% of the taken-up virus can be transmitted through BMVEC.[17,18] The second means is still very controversial because it is widely agreed that BMVECs only produce very limited HIV-1, if at all. CSF dissemination from a primary infection of CPx has been proposed as another possible mechanism partially supported by recent studies.[19,20] However, our studies,[21] together with others,[14,22] could not locate any productive HIV infection of the CPx both *in vivo* and *in vitro*. The *Trojan Horse hypothesis* is generally accepted due to the most compelling evidence.[15,16] The details of that model have been elucidated in many reviews.[23,24]

Although, HIV entry to CNS largely occurs via CCR5 co-receptor, the CXCR4 and CCR3 co-receptors are also reported to play a role in mediating HIV infection of brain. They are expressed in brain microglia although at lower efficiency than CCR5.[25] Moreover, HIV co-receptors CCR2, APJ, CX3CR1, STRL33/BONZO, and gpr1 are also expressed in the human brain although so far no defined role for them in mediating HIV CNS infection has been reported. However, CCR2, which is expressed on brain microvascular endothelial cells, has been reported to play a critical role for macrophage transendothelial migration in other neurological inflammatory disease,[26] suggesting that it might facilitate HIV-infected leukocytes to transmit through the blood brain barrier (BBB).

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Another study has shown HIV-1 variants isolated from the infected brain-derived CD4-positive cells expressed a CCR8/TER1, suggesting TER1/CCR8 can function as a co-receptor for HIV-1 CNS infection.[27] HIV co-receptor CX3CR1, expressed on microglia, is crucial for sustaining neuron-microglia communication and knockout of CX3CR1 can prevent neuron loss.[28] APJ is another co-receptor for some HIV-1 strains, which is expressed in the human brain and in NT2N neurons. Studies have indicated it might play a role in HIV neuropathogenesis.[29,30]

Impairment of blood brain barrier function in HIV-infected individuals

The alteration of BBB of HIV-1 infected patients has been detected either by MRI or single-proton emission computed tomography or is indicated by the leakage of serum protein, quinolinic acid, metalloproteinase and nitric oxide (NO) in the CSF.[31-39] The relative genomic and proteomic changes of HBMEC induced by HIV-1/HIV-infected monocyte-derived macrophages (MDM) have also been found.[40,41]

Alternation of the BBB function is not only a feature of HIV-1 CNS infection but it has a crucial impact on the pathogenesis of HAD,[32] because BBB usually only permits a small percentage of leukocytes to cross without disrupting its integrity, which preclude the circulating monocytes. Therefore, its impairment facilitates penetration of virus and influx of more activated and HIV-1 infected monocytes into the brain, which can spread virus to the resident glia cells, including microglia and astrocytes, and further disrupt the integrity of the BBB. The mechanisms of BBB dysfunction in the course of HIV infection are poorly understood. It has been reported that the plasma lipopolysaccharide (LPS), which can compromise the permeability of BBB, is significantly higher in HIV-1 progressors than LPS-injected HIV-1 seronegative human volunteers.[42] In addition, several cellular and viral factors have been demonstrated, including tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6), HIV-1 TAT and GP120, to influence the monocytes migration across the BBB directly or indirectly.[43-50] Cytokines and chemokines, such as IL-6, IL-10, IFN, CCL-2, CXCL-10, CXCL-1, CXCL-2, CXCL-5 etc., which are associated with the damage of microvascular integrity and the incidence of HAD, have been shown to be up-regulated in the brain and CSF of HIV-1 infected patients.[51-54]

The central nervous system as a site of HIV-1 reservoir

CNS has been regarded as one of the anatomical HIV reservoirs due to its immunologically privileged status. It is a huge challenge to overcome this difficulty and deliver therapeutic agents into the CNS, especially brain tissue, to treat the CNS disease. It has been reported that the CSF penetration rate of the nucleoside reverse transcriptase inhibitor AZT is 60% compared to the plasma level, and only 11% for 3TC.[55,56] Consistent with these reports, other studies have shown the CSF HIV has a slower decay rate, higher evolutionary rate and faster re-bounce rate compared to the HIV in plasma.[57-60] In addition, the data on viral genotypic evolution before and after HAART have both shown viral compartmentalization comparing HIV isolates from the CSF and plasma.[61-65] Although so far, very little information on intraparenchymal penetration rate of drugs is available, it has been well established that the brain tissue harboured unique sequences compared to the whole body.[13,66-68] Moreover, drug-resistant mutations in different areas of the brains have also been explored, suggesting compartmentalized evolution of HIV-1 in the brain.[69] In addition, the data on compartmentalization of HIV in the CNS support the belief that HIV infection of the brain contributes in part to the occurrence and pathogenesis of HIV associated neurocognitive disorders (HAND). This hypothesis also has been supported by the fact that some patients have poor CSF viral load control but good plasma viral suppression.[70] Further, the compartmentalization of HIV may have regional implications.[71]

The cellular reservoirs of HIV in the CNS are mainly microglia cells and macrophages. The role of each macrophage population in HIV spread and persistence depends on their turnover rate. Perivascular macrophages are assumed to be responsible for trafficking HIV between the periphery and the CNS, including dissemination of HIV from the peripheral blood to the CNS, commonly referred as the *Trojan horse* model; and reseeding CNS residing HIV strains back to the periphery.[72] In contrast, microglia has relatively longer turnover rate and it might play a more crucial role as HIV CNS reservoirs. Recently, the role of microglia in promoting HIV latency has been linked to the transcription factors, such as CTIP2, which can repress HIV-1 gene expression in microglia.[73,74] Moreover, variable levels of HIV-1 infections have been detected in other cell types within the CNS as well, such as: neurons, microvascular endothelial cells (MVEC) and astrocytes.[75] Recently, extensive astrocyte infection has been demonstrated in HAD patients and positive correlation degree between its infection frequency and the severity of neuropathological changes has been shown comparable to perivascular macrophages.[76] This suggests that astrocytes might play a crucial role as HIV reservoir.

HIV-associated neurocognitive disorders

HIV-associated neurocognitive disorders were recognized by clinicians shortly after the AIDS epidemic in 1981.[77] Identification of the retroviral aetiology of AIDS allowed introduction of the hypothesis that HIV-1 itself might affect the CNS and cause neurological disorders, referred to as AIDS dementia complex (ADC) or HIV-associated dementia (HAD).[78,79] The terms HIV encephalopathy, or HIV encephalitis, or HIV dementia are also commonly used.

Diagnostic criteria and current nomenclature

A diagnostic guideline was outlined by AIDS Task Force of the American Academy of Neurology (AAN) in 1991 proposing two levels disturbance:[80] HAD (Including HAD with motor symptoms, HAD with behavioural or psychosocial symptoms and HAD with both motor and behavioural/psychosocial symptoms), and minor cognitive motor disorder (MCMD). The specific criteria for reaching these diagnoses were provided as well. In 1995, this guideline was expanded by adding the diagnosis of *asymptomatic neurocognitive impairment*, which described mild neurocognitive deficits that do not substantially interfere with daily function but being recognized increasingly frequently.[81] Recently, a refinement of the AAN criteria was established by the HIV Neurobehavioral Research Centre at UCSD with the recommendation from an NIH working group.[82] These criteria include three diagnoses: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HAD (Supplementary Table 1). According to these criteria, at least five areas of well known HIV affecting neurocognitive functioning need to be assessed to arrive at the diagnosis. Apart from ideal comprehensive neuropsychological evaluation, a HIV dementia scale is used for assessing these domains due to its feasibility. In addition, the presence (or absence) of decline in everyday functioning is very important for the diagnosis of HAND. Unfortunately, to date, there are no widely agreed clinical measures of daily functioning,[83] thus the assessments of that mainly depends on self-report, using questionnaires such as Lawton & Brody's modified Activities of Daily Living scale and the Patient's Assessment of Own Functioning.[84,85]

Asymptomatic neurocognitive impairment and mild neurocognitive disorder

Asymptomatic neurocognitive impairment (ANI) refers to the mild neurocognitive deficits (MND) in two or more cognitive areas without a substantial interference in everyday functioning (Supplementary Table 1). It represents more than 50% of diagnosed HAND cases and 21-30% of the asymptomatic HIV-infected individuals.[86] Moreover, it has been reported to be well associated with HIV neuropathological abnormalities.[87,88] Thus, it will be particularly important to identify these cases and introduce intervention at this earliest stage of HAND for the best prognosis.

MND is marked by mild to moderate impairment in two or more cognitive areas in addition to mild to moderate decline in daily functioning. Based on the ANI criteria of MCMD, additional everyday functioning decline has been included. The incidence of MND remains high and the prevalence of MND has not changed despite the introduction of HAART.[82,89] Moreover, it has become more prevalent form since the severe forms of HAND are now not seen as frequently in the HAART era. The

prevalence of MND has been estimated at between 5-14% in individuals with early symptoms and approximately 25% of those with AIDS.[81,90] In addition, it has been reported that HAART failed to provide complete protection for MND from developing into HAD based on over more than 10 years of observations,[82,91-94] although other studies have shown that HARRT can temporarily deduce the incidence rate of MND in high risk populations.[95]

HIV-associated dementia

HAD is the most severe form of HAND in terms of its functional impact. It requires moderate-to-severe cognitive impairment in more than two areas with remarkable daily function declines and together with an additional abnormality of either motor function or specified neuropsychiatric/psychosocial functions, which cannot be explained by co-morbid conditions. In addition, sufficient consciousness must be retained for cognitive abilities assessment. Although the incidence of HAD has decreased dramatically after the introduction of HAART, antiretroviral drugs still fail to completely protect HIV-infected patients from developing HAD. Recently, the concerns about HAD are not only limited to its cause but the consequence as well, since HAD in the HAART era can signal patients' death.[96,97]

Epidemiology of HIV-associated dementia before and in the Era of highly-active antiretroviral therapy

HAD is one of the end-stage complications of HIV infection, which is not suppressed completely by HAART, although the incidence rate of HAD has declined dramatically. Before the HAART era, HAD affected almost 50-70% individuals with AIDS and became the most frequent neurological disorder at that time.[98] Since the introduction of HAART, the incidence rate of HAD dropped by almost 50% compared to early 1990s (Figure 1A).[99] However, the prevalence of HAD has stayed stable and even appears to be rising (Figure 1B) due to the longevity of HIV-infected patients on HAART. In addition, HAART has started to show its own neurological toxicity, which possibly also affects neurocognitive functions.[100-102]

Neuropathology before and in the era of highly-active antiretroviral therapy

Before HAART, the most significant of HIV associated neuropathology were HIV encephalitis (HIVE), opportunistic infections and/or primary CNS lymphomas.[103] HIVE is characterized by perivascular macrophage infiltration, multinucleated giant cells, activated microglias/microglia nodules, pronounced reactive astrocytosis, myelin pallor on microscopic sections and neuron loss.[78,104-108] Although the presence of HIVE correlates to HAD to some degree, the best correlates are macrophage infiltration, activated microglia and reduced synaptic/dendritic density and selective neuronal loss.[87,109]

After the introduction of HAART, the neuropathology of HIV infection and HAD has shifted.[87,94,110] Due to controlled plasma viral load levels and restored immune competencies after HAART, the opportunistic infections and primary CNS lymphomas declined dramatically.[111] So, there is a dramatic decrease in cerebral toxoplasmosis and cytomegalovirus (CMV) encephalitis, and more *burn-out* forms of HIVE are found, possibly part of the benefits from HAART.[112] However, the neuro-inflammation does not improve significantly and the extent of microglial activation is still comparable to pre-HAART era.[110] In addition, following HAART, a reversible HIV-associated amyotrophic lateral sclerosis (ALS)-like disorder has been observed.[113] Moreover, HAART influences HIV neuropathology by changing the predominant sites of involvement. In post-HAART era, the pronounced inflammation was found in the hippocampus and adjacent parts of entorhinal and temporal cortex, while basal ganglia is the most involved in pre-HAART era.[93,94,110] Furthermore, HAART causes immune reconstitution, which may lead to increased lymphocytic infiltration into the brain.[112,114] Several cases of immune reconstitution-related neuropathology, also called immune reconstitution inflammatory syndrome (IRIS), have been reported; characterized by massive lymphocytosis, extensive

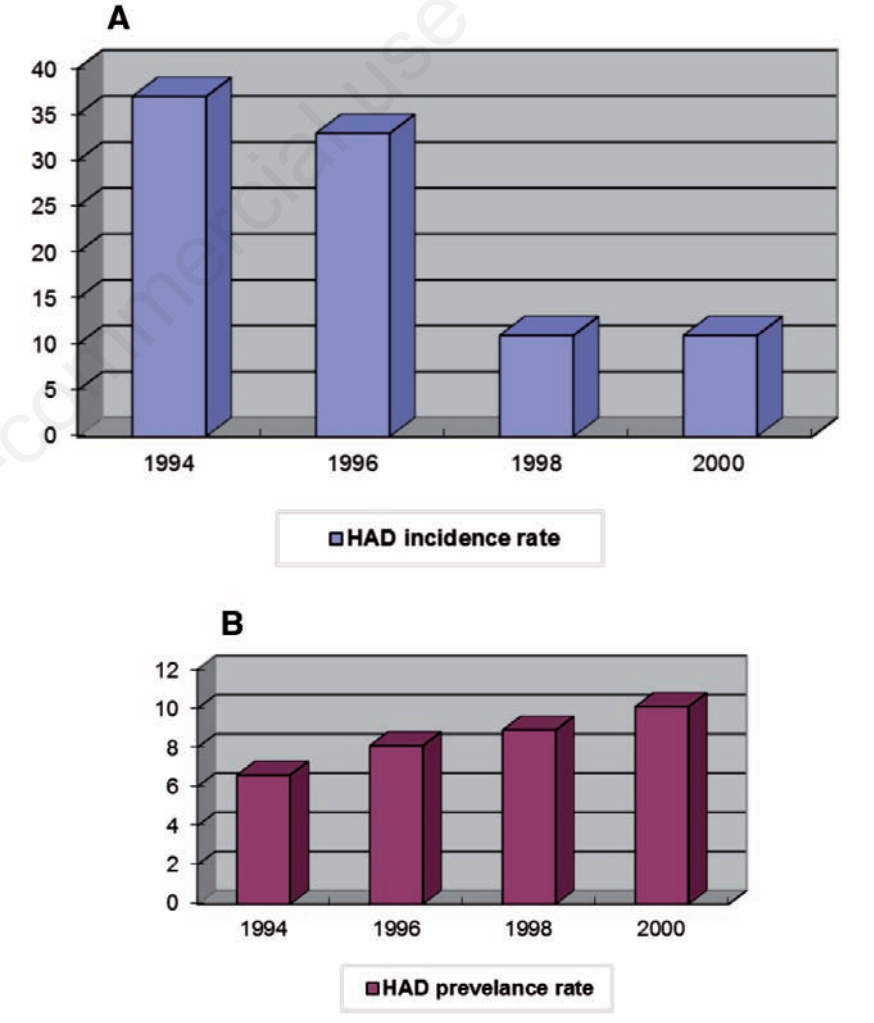

Figure 1. Incidence rate (A) and prevalence rate (B) of HAD in the Johns Hopkins HIV clinic. The *x*-axis corresponds to the calendar year. The *y*-axis corresponds to the incidence rate/prevalence rate per 1000 person years.

demyelination and white matter damage.[93,110] Peripheral neuropathies due to drug neurotoxicity are frequent.[115]

However, it is important to bear in mind that it is more difficult to organize the systematic neurological studies based on autopsies due to the longevity of HIV-infected patients after HAART. Hence, recent findings might not fully reflect the difference between pre-HAART and post-HAART, and also cannot represent those who survive from HAART but only HIV seropositive individuals who died following the failure of HAART. Besides, after HAART, a new chronic subtype of dementia has emerged among HIV+ patients together with the involvement of additional cognitive domains in previous phenotype,[116,117] partly due to the longevity of HIV seropositive patients after the introduction of HAART.

Possible pathogenesis of HIV-associated dementia

Viral factors

It has been well documented that productive HIV infection of the CNS is detectable on macrophage/microglia and astrocytes,[104,118] although so far infection of astrocytes is only limited to the transcriptional level or early expressed proteins (TAT, NEF and REV).[75,119-121] In addition, HIV proteins can be released from these HIV-infected cells and then exhibit their neuronal toxicity directly or indirectly, although neurons are not infected.[122-124] Three HIV proteins have been reported to cause direct neuronal injury or death: the virus's glycoprotein (gp120), trans-activator of transcription (TAT), and the viral protein R (VPR).

Gp120 is essential for HIV infectivity and has been shown to induce neuron apoptotic death using the CXCR4 receptor with and without the presence of glial cells in a dose-dependent manner,[125-128] and gp120 over-expression in transgenic mice can cause neuropathological similarity to that of HAD.[129] In addition, gp120 can also cause dysfunction of nigrostriatal dopaminergic system and injection to rat striatum result in neuronal apoptosis in the *substantia nigra*,[130] which might explain why dopaminergic neurons are more susceptible to gp120 neurotoxicity.[131] Neuronal injury or death induced by gp120 can be via interaction with N-Methyl-D Aspartate (NMDA) receptors,[127,132,133] which can influence the influx of Ca^{2+}, and therefore trigger further neuronal injury by harmful enzymes, as well as free radicals and additional glutamate.[67] Moreover, gp120 can also cause neuronal injury or death by interacting with apoptosis regulator, such as p38 mitogen-activated protein kinase,[134] or influencing the expression of pro-apoptotic transcription factor, such as E2F1.[135]

Another neurotoxic HIV protein is TAT, which is mainly active in nucleus and essential for HIV replication. *In vivo*, it has been shown to cause direct tissue loss when injected to the striatum of adult rats.[51] *In vitro*, TAT can cause dendritic loss and neuronal death at lower concentrations than those needed for viral replication.[136] The neurotoxicity of TAT has been supported by many other studies.[137-146] Interestingly, TAT neurotoxicity has regional preference, and some brain regions are more susceptible compared to others, such as the striatum, hippocampal dentate gyrus and the CA3 region of the hippocampus.[137,140,147] TAT can dysregulate neuronal microRNAs (miR),[148] which were found functioning in neurodevelopment and can mediate regulations of local synaptic and dendritic translation.[149] TAT can alter the tight junction protein expression and BBB function, which can promote brain infiltration. In addition, its neurotoxicity can also be through mediating mitochondrial energy metabolism failure, and therefore influencing normal synaptic communication;[150] activating p53 pathway and involving multiple intracellular-signalling pathways.[151-155]

Another HIV accessory protein is VPR, which is important for HIV initial infection and replication, and plays a role in HIV neurotoxicity as well. VPR can be detected from CSF of HIV seropositive patients, and may be involved in pro-apoptotic activity in AIDS-associated dementia.[156,157] Moreover, it has been shown that both intracellular and extracellular VPR is capable of inducing apoptosis in both rat and human neuronal cells, including the NT2 cell line, and mature and differentiated neurons by direct activation of the initiator caspase-8.[158-161] VPR neurotoxicity is possibly through several mechanisms: inducing cell cycle arrest at G2/M phase;[162] altering mitochondrial permeability;[163] regulating some apoptotic related proteins;[164,165] facilitating transporting of pre-integration complex, and promoting transcription.[166-169]

Other HIV proteins, such as NEF, REV and GP41, have also been reported to induce neurotoxicity. NEF is a known virulence factor or progression factor to AIDS,[170] which can manipulate infection, survival and replication of HIV.[171] In addition, NEF shares significant sequence homology with scorpion neurotoxins, which can inactivate potassium channels.[172-174] Consistently, NEF is lethal to neuron *in vitro* and abundantly expressed in astrocytes of HIV seropositive patients with pathological neuronal damage/dementia.[119,120,175,176] REV protein accumulates in the nucleus and exports unspliced RNA from nucleus to the cytoplasm.[177] It has been shown that REV has neurotoxicity *in vitro* and *in vivo*.[178] It has also been shown that HIV seropositive patients, with NEF and REV expressed in astrocytes, progressed most rapidly to severe dementia.[119] GP41 is also elevated in HAD patients, but *in vitro* studies showed it can only mediate neuronal injury in the presence of glial cells rather than directly.[179]

Role of mononuclear phagocytes

Apart from the direct neurotoxicity of HIV proteins, mononuclear phagocytes, including perivascular macrophages, resident microglia, etc. play a significant role in the development of HAD. First of all, as discussed above, macrophages have been proposed to traffic HIV into the brain and then infect/activate other macrophages or other cell types.[180] Actually, HIV proteins are predominantly released from infected macrophages since they are the major cell types supporting productive infection in the brain. Other than these, infected or activated macrophages can also release long list of soluble factors, such as cytokines, chemokines (see Cytokine and Chemokine sections), which have been implicated in the pathogenesis of HAD. Some studies have shown a better correlation between neurocognitive deficits and activated microglial cells than infection itself,[181] although we have recently shown that the direct and productive infection of the CNS macrophages is vital for HAD manifestation.[71] These disparate results might be due to the different sample sets, but the contribution of different disease progression pace appears more likely the cause. As a matter of fact, all human *in vivo* studies are based on autopsy brain samples, rather than *in vivo* tissue. Therefore, it is difficult to make any sole correlation between disease stage and possible pathological factors (such as HIV productive infection, or degree of cellular activation), because some patients progress too fast to show all HIV-related neurological stages before their death. So, disease progression pace would be a better parameter with which to correlate. We have found very extensive HIV productive infection in rapid progressors with relatively low cellular infiltration compared to those who progress more slowly. However, it is very hard to distinguish the role of HIV, activated systemic macrophages and activated CNS residential macrophages individually due to: i) HIV infection persists in the CNS, latently if not productively, after its initial entry at the very early stages of HIV infection; ii) microphage/microglia is the major cell type supporting productive CNS infection; iii) currently, there is no reliable marker available to separate perivascular macrophages and microglia.

Cytokines

Apart from direct HIV proteins neurotoxicity discussed above, soluble factors (such as cytokines, chemokines and their receptors) also play significant roles in the pathogenesis of HAD. Many neuronal injuries are mediated by cytokines and chemokines, which are secreted by HIV-infected or activated macrophage/microglia or astrocytes. It has

been reported that HIV-infected or activated macrophage/microglia can increase several pro-inflammatory cytokines expression, including TNF-α, IL-6, GM-CSF and IL-1β,[182-185] which can enhance CNS inflammation further. In addition, these cytokines have also been reported to upregulate in the CNS or CSF of HAD patients.[186,187]

Among them, TNF-α plays dual roles in HAD pathogenesis. It is a pro-inflammatory cytokine and also characterized as an oxidative stress mediator. It can stimulate reactive oxidative intermediates (ROIs) production in T cells,[188,189] and in turn cause T cell apoptosis, which has been proposed as one of the mechanisms of AIDS.[190,191] In addition, it can also cause apoptosis in human neuronal cells via similar mechanism and accelerate neurodegenerative disease pathology.[192] In contrast, some studies have also shown its neuro-protective role due to its capabilities to enhance anti-apoptotic and anti-oxidative protein expression.[193-197] These dual actions might be because of different inflammatory time course,[198] or different TNF receptors to which it binds.[199]

Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), a member of the TNF superfamily, has been shown to cause rapid apoptosis of different cells.[200-204] It increases in human monocyte-derived macrophages after HIV-1 infection and immune activation.[204-206] Moreover, it has been demonstrated that TRAIL-expressing macrophages are in close association with neurons undergoing apoptosis in HIV-1 encephalitis.[207] Interestingly, antibodies against TRAIL can dramatically prevent neuronal injury in both *in vitro* experiments and in an animal model of HIV-1 infection in the brain.[204,207] Worthy to note, different from TNF-α and IL-1β, TRAIL is preferentially expressed in HIV-infected macrophage/microglia.[207] All these results indicate that it contributes to macrophage-mediated neuronal loss in HAD.

Apart from TNF-α, all the other cytokines mentioned above have shown only indirect neurotoxicity. Interestingly, all of them can be related to TNF-α. M-CSF is majorly induced by TNF-α.[208] It can act on proliferation of cells of macrophage lineage, differentiation and survival and its antagonists have been shown to inhibit HIV replication in macrophages.[209,210] Therefore, it might contribute to cellular reservoir of HIV infection. IL-1β can upregulate TNF-α expression and IL-6 in mononuclear phagocytes, and also it can contribute to neuronal injury by promoting the expression of nitric oxide (NO);[211-213] IL-6 has to synergize with TNF-α to induce HIV expression at the transcriptional level, but not alone.[214]

Chemokines

HIV-infected or activated macrophages also secrete chemokines, which are a family of small chemotactic cytokines and can combine with their receptors and play important roles in immune surveillance and inflammatory process. Chemokines are essential compo-

Table 1. Role of selected chemokines and chemokine receptors in HIV-associated dementia.

Chemokine	Chemokine receptor	Location of receptor expression in brain	Effects in the brain
CXCL8 (IL-8)	CXCR1	Microglia, subsets of neurons, astrocytes and oligodendrocytes	Modulation of synaptic transmission and plasticity and inhibition of long-term potentiation in hippocampus*
	CXCR2	Microglia, neurons, astrocytes and oligodendrocytes precusrsors	
CXCL10 (IP10)	CXCR3	Microglia, subsets of neurons and astrocytes	Alteration of synaptic plasticity in hippocampus and induction of leukocyte infiltration
CXCL12 (SDF1α,β)	CXCR4	Microglia, neurons, astrocytes and endothelial cells	Promotion of neuronal migration during cerebella development, microglial chemotaxis and mesenchymal stem-cell migration to site of injury; promotion of survival or apoptosis of hippocampal neurons; regulation of cholinergic and dopaminergic systems; promotion of astrocyte proliferation; and promotion of cytokine and glutamate release
CCL2(MCP1)	CCR2	Human fetal glia and neurons, astrocytes and NT2N cells	Protection of neurons and astrocytes from NMDA- or HIV Tat-induced apoptosis, through release of astrocyte growth factors
CCL3 (MIP1α)	CCR1	Subsets of neurons, astrocytes and oligodendrocyte precursors	Development of CNS; migration of astrocytes and microglia; recruitment of monocytes to brain parenchyma in patients with HAD or other neurological disorders
	CCR5	Microlia, neurons and astrocytes	
CCL4 (MIP1β)	CCR5	Microglia, neurons and astrocytes	Recruitment of monocytes to brain parenchyma; involvement in migration of macrophages, microglia and astrocytes
CCL5 (RANTES)	CCR1 CCR3 CR5	Microglia, neurons and astrocytes	Recruitment of monocytes to brain parenchyma; involvement in migration of macrophages, microglia and astrocytes
CCL7 (MCP3)	CCR1 CCR2 CCR3	Microglia, neurons and astrocytes	Recruitment of monocytes to brain parenchyma
CX_3CL1 (Fractalkine)	CX_3CR1	Microglia, subsets of neurons, astrocytes and endothelial cells	Recruitment of receptive cells (mainly microglia), when in soluble form; polymorphisms affect the development of AIDS

*Long-term potentiation is a persistent increase in the size of the synaptic response that is induced by several mechanisms; in the hippocampus, it is thought to be the synaptic basis of learning and memory in vertebrates. CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; CNS, central nervous system; CSF, cerebrospinal fluid; CXCL, CXC-chemokine ligand; CX3CL1, CX3C-chemokine ligand 1; CXCR, CXC-chemokine receptor; CX3CR1, CX3C-chemokine receptor 1; HAD, HIV-associated dementia; IL, interleukin; IP10, interferon-γ-induced protein of 10 kDa; MCP, monocyte-chemotactic protein; MIP1, macrophage inflammatory protein 1; NMDA, *N*-methyl-D-aspartate; RANTES, regulated upon activation, normally T-cell expressed and presumably secreted; SDF1, stromal-cell-derived factor 1; SHIV, simian-human immunodeficiency virus; SIV, simian immunodeficiency virus; Tat, transcriptional transactivator; TNF, tumour-necrosis factor. Taken from Gonzalez-Scarano *et al.*[107]

nents for normal neuronal physiology in the CNS. However, the over-expression of some chemokines can lead to excess activated leukocytes infiltration into the CNS and consequently to neuronal injury, while others exhibit neuroprotective function. So, the balance between their neuro-protection and neuro-degeneration roles are crucial to HAD pathogenesis. Not surprisingly, altered expression of chemokines and chemokine receptors has been found in HAD brain,[215-217] indicating their involvement in HAD pathogenesis. However, their contribution still remains unclear. So far, CC chemokines have not shown any neurotoxicity, but only neuroprotective roles *in vitro*, such as RANTES and MIP-1β,[128,218,219] while CXC chemokines have been found to be neurotoxic, such as IP10 and SDF-1.[220-222] Table 1 shows the detailed effects of selected chemokines and chemokine receptors in relation to HAD.

Other soluble factors

HIV-infected or activated macrophages also secrete other soluble factors which have been reported to be neurotoxic, including L-cysteine,[223] quinolinic aicd,[224] neurotoxic amine NTox,[225] NO,[226] and eicosanoids.[184] Their neurotoxicity are all mediated or related to glutamate. The neurotoxic effects of L-cysteine, quinolinic aicd and NTox are all NMDA receptor directed.[227-229] Some eicosanoids expression altered upon HIV infection as well, such as arachidonic acid and PAF,[230] a metabolite of arachidonate.[184,231] PAF can be rapidly produced by HIV-infected mononuclear phagocytes and it has been reported to mediate the release and activation of glutamate.[232,233] Of NO, although the most of the neurotoxic actions are mediated by peroxynitrite (ONOO-), the reaction product from NO and superoxide anions, still partly contribute to glutamate neurotoxicity in primary neuronal cell cultures and in animal models of stroke.[234] In addition, it has been proven that glutamate is the predominant neurotoxic factor released from activated macrophage/microglia.[235]

DNA microarray and its applications to HIV-associated dementia

It is well known that host genetics plays a role in the aetiology of neurodegenerative disease, including HAD. Thus, it is necessary to study host genetics in order to define host-viral interaction and understand the genetic basis of disease. First of all, the gene expression products are critical for the normal development, function and adaptive response of the nervous system,[236] and minor fluctuations or

Table 2. Gene profiling studies in HIV-1 infected astrocytes and HIV-1 or SIV infected brains.

Sample source	Microarray	Experiment design	Conclusion	Ref.
		Astrocytes		
Primary human astroyctes	NIA immuno and neuroarray	HIV *vs* non- HIV HIV-gp120 *vs* non- HIV-gp120	Differential effect of HIV-1 and gp120 in astrocytes. Gp120 has more profound effect but chemokine and cytokine induction occurs predominantly by HIV infection	249
Primary human astroyctes	Affymetrix U133 A/B	VSV-HIV *vs* non- VSV-HIV	Up-regulation of IFN antiviral responses, intercellular contacts, cell adhesion, and signalling. Down-regulation of cell cycle, DNA replication, and cell proliferation	250
Astrocytoma	BD bioscience clontech	Native Nef *vs* non-myristoylated Nef	Up-regulation of small GTPase signalling, regulation of apoptosis, lipid metabolism, JAK/STAT and MAPK signalling pathways	251
		Brain tissue		
Macaque-basal ganglia	Clontech chemokine and cytokine array	SIVE *vs* non-SIVE	Upregulation in SIVE of genes involved in promoting macrophage infiltration, activation and virus replication. Down regulation of genes regulating neurotrophic functions	255
Macaque-frontal lobe	Affymetrix U95Av2	SIVE *vs* ni	Up-regulation in SIVE of genes implicated in monocyte entry to the brain, inflammation, IFN response, antigen presentation, production of neurotoxic effects, transcription factors and others Up-regulation in acute SIV infection of genes involved in IFN and IL-6 pathways. Many of these genes also up-regulated in long-term infection and SIVE	256 257
Macaque-cortical brain	Clontech cytokine array	SHIV *vs* ni	Up-regulated genes, including Cripto-1 and genes implicated in inflammatory, neuroprotective, cognitive, and stress responses	258
Human-frontal cortex	Affymetrix U95Av2	HIVE *vs* non-HIVE	Up-regulated pathways included neuroimmune and antiviral response, transcription factors, and cytoskeletal components	253
Human brain cortex (middle frontal gyrus)	Affymetrix HG-U133	HAD *vs* non-HIV	The analysis focused on ionic conductance carriers that control membrane excitation. They found six ionic channel genes overexpressed in HAD brains compared to control while seven downregulated. Conclude the relevance between channelopathy and subcoritcal dementias.	252
Human-frontal cortex	Affymetrix human genome U95A	HIV-1 infected and 4 HIV-1 negative control subjects	Focusing on analytic approaches	254

Modified from Sui *et al.*[255]

alterations in gene expression can influence the susceptibility of the host to neurological disorders, including attention deficit disorder, and schizophrenia,[237] PD and AD,[238] as well as HAD.[239] Therefore, genetic studies will offer a direct clinical impact on HAD in terms of diagnosis and pre-symptomatic testing. Consequently, it will shed light on broader genomic aspect of pathogenesis of HAD, which is not limited on individual genes or genetic forms, but to provide potential target pathways for therapy. In addition, these studies have the potential to contribute to the development of effective animal model to study HAD and other neurodegenerative diseases.

DNA microarray has become the most popular tool for global gene expression study. It is characterized by high-density arrays of DNA oligonucleotides bonding to a structural support, which differ with types of arrays (*e.g.* a solid surface, such as glass, plastic or silicon biochip or coded beads). The core principle behind microarrays is hybridization between target samples and probes, then based on different labeled target (*e.g.* fluorophore-, silver-, or chemiluminescence-labeled), these hybridizations can be detected and quantified by relative abundance of nucleic acid sequences in the target. It can be used to detect either DNA or RNA (most commonly as cDNA) that may or may not be translated into proteins. One of the greatest advantages of these methods is that they allow the analysis of thousands genes in relation to specific disease in one experiment. Gene expression profiling is one of the applications of DNA microarray to identify genes whose expression is changed in response to pathogens or other stimulating factors.

Since the first microarray-based study in gene expression of host cells in relation to HIV infection,[240] a variety of different types and generations of microarrays have been applied to HIV viral-host interaction studies, and to HAD pathogenesis as well. However, most of them have been done on glial cells because of the difficulties of analysing multiple cell types from brain rather than clonal expansion of a single-cell type, and accessing the relevant tissues during the lifetime of the patient.[241] In addition, because astrocytes constitute 50-60% of brain cell volume,[242] they have been chosen as a target cell type by many researchers. Although only a very small astrocytic population can be infected *in vivo* by HIV and even *in vitro*,[243-245] the infection is passive and not cytolytic,[246,247] astrocytic function can be altered by binding HIV-1 or envelope protein gp120, which is consistent with changes in gene expression.[248] Among those studies, several are comprehensive gene expression profiling of astrocytes exposed to HIV-1 or viral proteins using high-flux microarray platforms for parallel detection of multiple differentially expressed genes.[249-251] The details are listed in Table 2.

Apart from cells, several microarray studies have been carried out in different brain regions of macaques with and without SIV encephalitis (Table 2). Moreover, limited genomic studies (partial human genome) on human brain tissues from patients with and without HIV-associated CNS disorders have also been done.[252-254] The details are listed in the Table 2.[255-258] Interestingly, there are considerable number of consistently dysregulated genes in human astrocytes and in macaque and human brain, which might suggest the important role that HIV-infected or activated astrocytes play in HAD pathogenesis. The common genes are mostly implicated in immune responses, and neurological function/diseases. Although many *in vitro* and *in vivo* studies have been done, so far the whole genome microarray fingerprint profiling using autopsy human brain tissue is still lacking.

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