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Evolving paradigms in the pathogenesis of HIV-1-associated dementia

Tracy Fischer-Smith and Jay Rappaport

HIV-1-associated dementia (HIV-D) remains a significant consequence of HIV-1 infection and AIDS. Since the clinical introduction of highly active antiretroviral therapy (HAART), the incidence of HIV-D has decreased, yet the prevalence has increased as patients are living longer under treatment. Additionally, a less severe form of HIV-D, minor cognitive motor disorder, has become an increasing issue. Two different models have been proposed for virus entry in the central nervous system (CNS) in HIV-D. In the 'Trojan horse' model, the virus enters the CNS early carried by macrophages and infects resident glia; later in the course of infection, virus replication is activated and additional monocyte/macrophages are recruited into the CNS via cytokine/chemokine networks and endothelial-cell–leukocyte interactions at the blood–brain barrier. In the 'late invasion' model, an inherently invasive activated monocyte subset is expanded from bone marrow as a result of immune dysregulation in the periphery in the setting of AIDS. In this review we discuss these two separate, although not mutually exclusive, means for virus entry and persistence in the CNS. Additionally, we explore mechanisms for neuronal injury and apoptosis, including the role of virus, viral and host proteins, oxidative stress and products of infected or uninfected activated microglia and astrocytes. Potential therapeutic strategies are also briefly discussed.

Human immunodeficiency virus type 1 (HIV-1)-associated dementia (HIV-D) is a syndrome of motor and cognitive dysfunction observed in approximately 10% of patients infected with HIV-1 with acquired immune deficiency syndrome (AIDS) (Refs 1, 2). Symptoms of HIV-D can range from mild (where patients present with moderate psychomotor slowing) to severe motor

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and cognitive disorders sometimes leading to loss of consciousness, coma and even death. The neuropathogenesis of HIV-D remains incompletely understood. Viral infection of the central nervous system (CNS) does not appear to be sufficient for the induction of disease; HIV-1 infects the brain early during acute infection yet little virus is generated and retained in the CNS until late in the disease process (Refs 3, 4). In children, severe clinical dementia has been observed in the absence of evidence of HIV-1 replication in the CNS (Ref. 5). Instead, a better correlate for the severity of HIV-D appears to be the number of brain mononuclear phagocytes, which include perivascular macrophages and microglia in the CNS, rather than the amount of virus or the number of infected cells.

Microglia cells, the resident macrophage of the brain, populate the CNS during fetal development and for a brief period after birth, after which, repopulation and turnover of this population is extremely slow (Ref. 6). By contrast, perivascular macrophages, found adjacent to blood vessels in the CNS, are continuously replaced by monocytes from the circulation (Ref. 7), thereby connecting the CNS with the peripheral immune system (Ref. 8). These two cell types represent the only cells in the CNS that have consistently and convincingly been demonstrated to harbour productive HIV-1 infection (Refs 9, 10, 11, 12). Direct or indirect activation of these cells by HIV-1 infection is believed to play a key role in the neuropathogenesis of HIV-D.

Numerous studies and review articles have explored the mechanisms by which activated and/or infected macrophages/microglia secrete viral proteins and/or toxic metabolites leading to neuronal injury via direct and indirect mechanisms (Refs 13, 14). Additional studies and corresponding review articles have explored the cytokine and chemokine networks that recruit monocytes/macrophages into the CNS. In addition to summarising these findings, this review explores an alternative mechanism where events in the periphery play a more prominent role: we discuss the notion that virus replication, CD4 depletion, immune activation and finally the expansion of an activated monocyte subset in circulation lead to CNS invasion. We anticipate that a more complete understanding of the mechanisms by which HIV-1 contributes to the development of HIV-D, including events outside the CNS, may lead to new therapeutic strategies as well as surrogate markers for the treatment and management of HIV-1 infection and its neurological manifestations.

Neuropathology of HIV-D

HIV encephalopathy (HIVE), the neuropathology of HIV-D, is usually observed late in the progression of AIDS and is characterised by the presence of widespread reactive astrocytosis, myelin pallor on microscopic sections (which indicates deficient myelin) and the infiltration of mononuclear phagocytes into the CNS compartment. Neuroimaging of HIV-D patients reveals a generalised white-matter reduction, with additional grey-matter loss localised to the basal ganglia and posterior cortex (Refs 15, 16). Microglial nodules and multinucleated giant cells, both hallmarks of HIVE, are generally located proximal to blood vessels and are associated with areas of white-matter degeneration and regions of necrosis (Ref. 17). The accumulation of perivascular macrophages around CNS blood vessels in the form of 'cuffs' has been well described (Refs 9, 10).

Incidence of HIV-D in the HAART era

In the USA, the introduction of highly active antiretroviral therapy (HAART) has resulted in an initial decrease in the number of new HIV-D cases (Refs 1, 2). HAART was introduced into clinical practice in the USA in 1996 with the approval of indinavir and ritonavir by the Food and Drug Administration (FDA) (Ref. 18). Although HAART has reduced the incidence of HIV-D, the prevalence has risen, reflecting the fact that HIV-1-infected individuals are now living longer with AIDS (Refs 1, 19). HIV-1-associated sensory neuropathies have also increased in prevalence, possibly partly as a result of neurotoxicities associated with HAART (reviewed in Ref. 20).

It has been proposed that HIV-D results from the replication of HIV-1 in the brain as an independent reservoir of virus infection (Ref. 21), yet the protease and reverse transcriptase inhibitors that make up HAART penetrate the blood–brain barrier (BBB) poorly and at subtherapeutic levels (Ref. 22). Nevertheless, successful HAART therapy results in improved motor and cognitive function and has even reduced the incidence of HIV-1-associated neurodegenerative diseases (Refs 23, 24). In children, HIVE has been shown to be a reversible

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manifestation of HIV-1 infection, responding to HAART and relapsing upon loss of control of plasma viraemia (Ref. 25). These findings suggest that interrupted virus production in the circulation and restored immune function lessen the occurrence of HIV-D and, as such, that events outside of the CNS contribute to the pathogenesis of HIV-D. There might be some instances, however, where immune reconstitution as a consequence of HAART results in CNS lymphocytic infiltrates (Ref. 26). After HAART, there also appears to be an increased prevalence of minor HIV-1-associated cognitive impairments (Ref. 26).

Models for virus entry and persistence in the CNS

Virus entry into the CNS ensues early during the course of infection and is proposed to occur by several means, including: infection of brain capillary endothelial cells (Refs 27, 28); passage through the blood–cerebral spinal fluid (CSF) barrier of the choroid plexus (Refs 29, 30); and/or transport of virus across the BBB by infected monocytes/macrophages (Ref. 31). During the early phase of infection, after the peak of acute viraemia, cells productively infected with HIV-1 are killed by cytotoxic T cells (Refs 4, 32). Despite early control, however, the virus ultimately appears to establish a productive infection and persistence in the CNS, eventually leading to the development of HIV-D in some individuals. Indeed, several studies have correlated viral load in the CNS and CSF with the severity of dementia (Refs 33, 34, 35). It is not yet clear whether virus in the CNS recrudesces from dormant infected cells entering early in infection or is derived from newly invading cells entering the CNS later during the course of HIV-1 infection. Accumulating evidence discussed in this review, however, supports the latter model.

The 'Trojan horse' model

The Trojan horse model maintains that virus that enters the CNS during acute infection establishes a life-long persistence in the CNS where it is able to replicate and evolve in a protected reservoir, potentially leading to a viral phenotype that promotes the development of HIV-D. While HIV-1 clearly enters the CNS early, there is somewhat of a paradox that the HIV-1-induced CNS disease is usually a late event in association with $CD4^+$ T-cell depletion and AIDS. Additionally, virus that enters the CNS during the acute phase of infection appears to be controlled and/or cleared by $CD8^+$ T-cell responses. Interestingly, $CD8^+$ T-cell depletion results in rapid-onset encephalitis in macaques after simian immunodeficiency virus (SIV) infection (Refs 36, 37). Other studies in the SIV model, however, suggest a persistence of HIV-1 proviral DNA during a quiescent phase, and the recrudescence of virus replication late in the course of SIV disease (Refs 38, 39). This model seems to require a state of CNS viral latency, and HIV-1 within the CNS compartment has been proposed to play a role in the development of HIV-1-induced CNS disorders.

The identification of divergent drug-resistant HIV-1 quasispecies in paired CSF and plasma viral isolates during antiretroviral therapy (Refs 40, 41) prompted the suggestion of compartmentalised evolution of HIV-1 in the CNS. This supports the view that virus entering the CNS early is contributory in the pathogenesis of HIV-D. Additionally, a recent study found similar discordance, as well as the simultaneous partitioning of V3 sequences from patients with advanced immune suppression who had failed or had stopped antiretroviral therapy (Ref. 42). The appearance of independent viral evolution in the two compartments, however, might reflect the fact that different cell populations normally contribute to the pool of virus recovered from plasma and the CSF. Moreover, only half of the subjects investigated in one study showed discordance in viral drug-resistance mutations (Ref. 41), and a separate study reported identical resistance patterns to HIV-1 nucleoside reverse transcriptase inhibitors in the CSF and plasma in 21 out of 31 subjects studied (Ref. 43). It is unlikely that selection of drug-resistant variants occurs in the CNS, particularly since antiretroviral drugs penetrate the CNS poorly. Additionally, it should be recognised that the perivascular macrophages in CNS are probably derived from circulating peripheral blood mononuclear cells (PBMCs), whereas plasma viraemia is derived from virus-producing cells in lymphoid tissues (Refs 44, 45). Since PBMCs and plasma show different kinetics for the appearance of drug-resistance mutations, it is not surprising that plasma and CSF viruses show different patterns of antiretroviral-drug-resistance mutations, and the difference in sequence distribution alone does not necessarily argue for compartmentalised evolution of HIV-1 in the CNS.

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Some sequencing studies comparing virus recovered from whole visceral and brain tissues demonstrated sequences unique to the CNS (Refs 21, 29, 46) and provide further support for the idea that the CNS provides a sanctuary for viral replication and evolution. Other studies, however, have shown viral sequences that cluster closely together or are common to the CNS and viscera (Refs 47, 48). These seemingly opposing interpretations of the data might reflect the differing distribution of HIV-1-infected cell types (macrophages and/or T cells) in the tissues examined. A recent study investigating drug-resistance mutations in different areas of the CNS demonstrated primary and secondary drug-resistance mutations that showed regional compartmentalisation within the CNS of HIV-1-infected individuals with and without dementia (Ref. 49). The identification of these sequences within the CNS and their regional differences might suggest compartmentalised evolution of HIV-1, or alternatively region-specific entry of available quasispecies at different time periods during the course of disease. The authors proposed that the suboptimal drug concentrations in the CNS might contribute to selection, escape and evolution, possibly providing a source of drug-resistant virus for release into the periphery. The co-prevalence of nonmutant virus in addition to a similar degree of noncanonical mutations that do not confer drug resistance (Ref. 49) might also suggest differences in when virus entered the CNS rather than evolution as a mechanism to explain the region-specific sequence diversity observed. In a separate study aimed at determining the relationship of virus recovered from the basal ganglia, choroid plexus and spleen found that virus from the choroid plexus was most similar, although distinct, to that found in the brain (Ref. 50). Isolates were also recovered with high similarity to those found in the periphery. These findings support a role for trafficking between and differential selective pressures within the tissues examined.

The 'late invasion' model

An alternative hypothesis, which we favour, suggests that the development of HIV-D begins outside of the CNS compartment, independent of virus that might already be present in the brain (Refs 51, 52). In this model, an altered cytokine environment resulting from chronic immune deficiency leads to the development of an activated monocyte subset that is more invasive. These activated cells, some of which harbour productive virus, enter the CNS compartment. Once in the CNS, infected and/or activated macrophages/microglia produce cellular and/or viral factors that contribute to neuroglia activation and/or are directly or indirectly neurotoxic.

In support of this hypothesis, patients with HIV-D have greater numbers of circulating monocytes that express CD14 and CD16 when compared either with AIDS patients without dementia or seronegative individuals (Ref. 51). These cells also appeared to be activated as demonstrated by their expression of the early activation marker CD69 (Ref. 51). All leukocytes express specific cell-surface antigens, designated cluster of differentiation (CD) antigens, and these reflect either different stages of their lineage-specific differentiation or different states of activation or inactivation. All circulating monocytes are $CD14^+$, and a minor subpopulation also expresses the activation marker CD16 in healthy individuals (Ref. 53). This $CD14^+CD16^+$ subset represents an activated monocyte subset that is largely expanded during acute and chronic infectious or non-infectious inflammatory diseases (Refs 54, 55). $CD14^+CD16^+$ monocytes exhibit features of tissue macrophages, are more phagocytic than $CD14^+CD16^-$ cells and express higher levels of tumour necrosis factor α (TNF-α), interleukin (IL)-1 and major histocompatibility complex (MHC) class II antigens (Ref. 54). It has been proposed that $CD14^+CD16^+$ cells are more invasive, allowing these cells to compromise the BBB and enter the CNS compartment (Ref. 52). In support of this, a recent study has demonstrated that HIV-1-infected individuals with a high viral load had a significant increase in monocytes expressing CD16, as well as CCR5 and monocyte chemoattractant protein 1 (MCP-1) proteins, which are involved in chemotaxis (Ref. 56). Additionally, greater expression of adhesion molecules, such as very late antigen (VLA)-4 and CD11b, on this expanded monocyte subset might also contribute to monocyte/macrophage invasion of the CNS. Endothelial cell adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1, which binds VLA-4 and is expressed significantly in HIV-D (Ref. 57), might also facilitate this entry.

The number of activated mononuclear phagocytes in the brain is reportedly a better correlate of HIV-D than the level of virus in the CNS

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(Ref. 58). An accumulation of $CD16^+$ perivascular macrophages in the CNS has been demonstrated in HIVE (Ref. 59) and in the simian equivalent, SIVE (Ref. 37). CD14 and CD45 (leukocyte common antigen) expression is detectable in perivascular macrophages, but not in resident microglia, using standard immunohistochemical methods (Refs 60, 61, 62, 63). The $CD16^+$ perivascular cells observed in HIVE appear to have recently entered the CNS compartment from the periphery, as shown by expression of CD14 and CD45, and are the major reservoir of productive viral infection in the CNS (Ref. 59). Furthermore, invasion or trafficking of cells from the periphery is supported by the finding that the increase in the number of mononuclear phagocytes does not appear to be due to proliferation (Ref. 64).

Interestingly, HAART restores a normal pattern of cytokine expression and significantly decreases the expansion of the $CD16^+$ monocyte subset (Ref. 65). This might imply that the decrease in the incidence of HIV-D seen following HAART therapy is perhaps a result of its ability to control monocyte activation through control of HIV-1 infection, as well as to improve immune function. The reversible component of HIV-D with successful therapeutic application of HAART supports this view, particularly since antiretroviral drugs penetrate the BBB poorly (Ref. 22). A recent clinical neuroimaging study demonstrated correlation between BBB compromise and plasma viral load, as well as neurocognitive impairment (Ref. 66). In patients undergoing HAART treatments, the effects on the BBB were significantly reduced. This level of protection could be due to changes in virus production and/or reduced monocyte/macrophage invasion of the CNS.

An additional cell-surface marker that has been associated with HIVE/SIVE is CD163 (Refs 67, 68), a haemoglobin scavenger receptor found exclusively on circulating monocytes and specific tissue macrophages (Ref. 69). Interestingly, CD163 has been demonstrated to be expressed by perivascular macrophages but not resident microglia in normal brain (Ref. 72) In our own studies in HIVE (J. Rappaport et al., unpublished) and those reported by Roberts et al. in SIVE and HIVE (Ref. 68), cells with ramified microglial morphology are prominently positive for CD163. This might further suggest that the increased numbers of microglial cells in HIVE/SIVE are due to CNS engraftment of perivascular macrophages moving into the brain parenchyma and taking on microglial characteristics. Since CD163 is absent from parenchymal microglia in other CNS disorders (Ref. 72), it is unlikely that expression in HIVE/SIVE is due merely to resident microglial activation. The expression of CD163 on macrophages differentiated in the presence of macrophage colony-stimulating factor (M-CSF), but not granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-4 (Ref. 73), supports a mechanism where monocytes from bone marrow and circulation give rise to monocytes/macrophages entering the CNS as perivascular macrophages.

The urokinase-type plasminogen activator system might also play a role in monocyte/macrophage trafficking. Soluble urokinase plasminogen activator receptor (uPAR) is increased in the CSF of patients with HIV-D (Refs 74, 75). Similarly, macrophages/microglia stain positively for uPAR in brains specimens from these patients. These results emphasise the potential role of extracellular matrix degradation and cell migration in the process of monocyte/macrophage invasion of the CNS in HIVE.

Neuronal injury and apoptosis in HIV-D

Productive viral infection has not been demonstrated in neurons in vivo, but there is some evidence to suggest that HIV-1 does enter neurons to a limited extent. HIV-1 Nef and Gag gene sequences have been detected infrequently in microdissected pyramidal neurons from the hippocampus (Ref. 76). In view of the paucity of infected neurons in HIV-D and the abundance of infected macrophages, microglia and astrocytes, the most significant contribution to neuronal injury and apoptosis in HIV-D probably occurs indirectly through the action of soluble factors produced by infected and/or activated mononuclear phagocytes and astrocytes. The roles of viral and toxic factors released from activated and/or infected macrophages/microglia in neuronal injury and apoptosis have been extensively studied and reviewed (Refs 13, 14, 26, 77, 78, 79, 80, 81, 82, 83, 84, 85). Several mechanisms have been proposed based on in vitro and tissue-based studies, including: excitotoxin and free-radical generation (Refs 86, 87); mononuclear-phagocyte-mediated alterations in the BBB (Ref. 88); interaction of HIV-1 envelope proteins with chemokine receptors (Refs 89, 90, 91); interactions of cytokines with the death receptors TNF-α, Fas and TNF-related apoptosis-inducing ligand (TRAIL) (Refs 82, 92);

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and *N*-methyl-D-aspartate (NMDA) receptor-induced neuronal injury in response to the excitatory amino acids (EAAs) L-cysteine or glutamate, which is increased through several mechanisms involving activated macrophages and viral proteins .

NMDA receptors are coupled ion channels that allow influx of Ca^{2+} ions in response to glutamate. Overstimulation of this receptor promotes excessive influx of Ca^{2+} in neurons, triggering a variety of potentially harmful enzymes, as well as formation of free radicals and additional release of glutamate. The excess glutamate subsequently stimulates NMDA receptors on neighbouring neurons, initiating further injury. Activated and/or infected monocyte-derived macrophages produce excess extracellular glutamate in vitro, providing an additional mechanism for neuronal injury (Ref. 93). Furthermore, HIV-1 Tat protein and TNF-α have been demonstrated to act alone and synergistically in impairing the ability of astrocytes to take up and metabolise excess glutamate (Ref. 94), thereby interfering with the normal role of astrocytes in protection from neuronal injury. Arachidonic acid release by activated and/or infected macrophages further impairs astrocytic uptake of extracellular glutamate (Ref. 95), which might be further compromised by HIV-1 infection of astrocytes or indirect pathways involving cytokine dysregulation. L-cysteine is another molecule toxic to neurons via NMDA receptors, with increased release in response to HIV-1 gp120 and inflammatory cytokines TNF-α and IL-1β (Ref. 96) (Fig. 1).

Apoptotic neurons (Refs 97, 98) as well as astrocytes (Ref. 99) have been demonstrated in patients with HIV-1 infection and HIV-D. The number of apoptotic neurons, however, does not correlate with the level of CNS inflammation or the severity of dementia (Ref. 100), although topographically, multinucleated cells have been observed in the vicinity of apoptotic neurons in the basal ganglia. Since apoptosis of neurons does not correlate with the location of HIV-1-infected cells, the contribution of soluble factors has been suggested (Ref. 97). Numerous in vitro studies suggest products from macrophages can induce neuronal apoptosis. It should be recognised, however, that the macrophages/microglia are localised primarily within the white matter. From this location, axonal degeneration would be an important mechanism for neuronal injury. In support of this notion, alterations in neuronal dendritic arbour have been observed in HIV-D brain (Ref. 101). It has been proposed that neuronal apoptosis is secondary to axonal damage and oxidative stress. Neuronal apoptosis is therefore a late event that does not seem to be the primary cause of HIV-D, which exhibits initially reversible properties upon antiretroviral treatment (Ref. 102).

Role of mononuclear phagocytes in HIV-D pathogenesis

As discussed above, virus entry into the CNS has been proposed to involve trafficking of HIV-1-infected monocytes/macrophages from the circulation (Ref. 31). Once in the brain, infected macrophages can infect other perivascular macrophages or microglia and/or stimulate these cells through the release of soluble factors such as cytokines, chemokines, viral proteins and EAAs. These factors have been implicated in the development of HIV-D as a result of their ability to promote further activation of uninfected mononuclear phagocytes, recruit additional mononuclear phagocytes into the CNS compartment, overstimulate astrocytes, and induce neuronal dysfunction and/or apoptosis (Refs 13, 14). In accordance with this, neuronal apoptosis has been found to correlate with microglia activation where apoptotic neurons are seen largely in the vicinity of multinucleated giant cells and/or mononuclear phagocytes showing productive infection (Ref. 100).

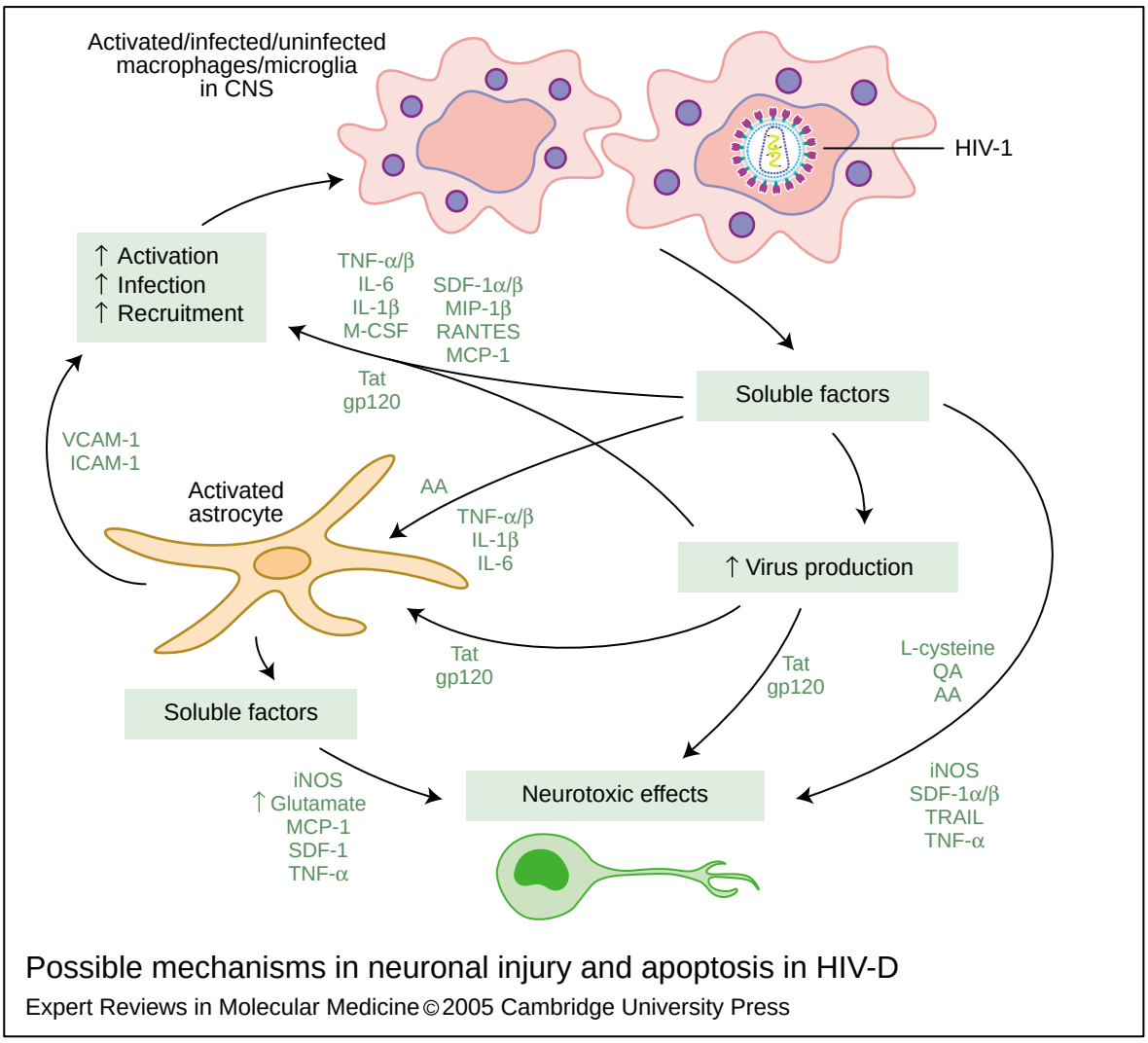
Cytokines

Several pro-inflammatory cytokines have been reported to be elevated in the CNS and/or CSF of patients with HIV-D, including TNF-α (Ref. 103), IL-6, GM-CSF (Ref. 104) and IL-1β (Ref. 105). These are probably released from infected and/or activated perivascular macrophages and resident microglial cells. Although viral infection and/or stimulation of mononuclear phagocytes by shed viral proteins has been demonstrated to increase expression of these pro-inflammatory cytokines (Refs 106, 107, 108, 109), the elevated levels do not appear to be the sole result of HIV-1 infection, but rather reflect the additional effects of endotoxin and cytokine and/or chemokine stimulation (Refs 110, 111, 112). Once initiated, many of these cytokines can augment expression through autocrine and paracrine mechanisms, enhancing a pro-inflammatory environment in the CNS.

With the exception of TNF-α, which can be directly neurotoxic (Ref. 113), these cytokines

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Possible mechanisms in neuronal injury and apoptosis in HIV-D

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Figure 1. Possible mechanisms in neuronal injury and apoptosis in HIV-D. Neuronal injury is likely to occur indirectly through factors secreted by infected and/or activated macrophages/microglia and astrocytes. For example, the cytokines TNF-α, IL-6 and IL-1β can act in an autocrine or paracrine manner to further augment cytokine and chemokine production, as well as production of virus through induction of nuclear factors that can act on the viral long terminal repeat (Fig. 2). Additionally, cytokines can promote production of metabolites, such as iNOS, that may cause neuronal injury or loss. Chemokines, including SDF-1α/β, MIP-1β, RANTES and MCP-1 may recruit additional macrophages into the CNS. SDF-1α/β can directly promote neuronal injury. Astrocytes might further contribute to the to the influx of monocytes/macrophages through upregulation of VCAM-1 and ICAM-1 in response to cytokines and Tat. TRAIL may contribute directly to neuronal apoptosis. Virus and shed viral proteins, including gp120 and Tat, promote additional cytokine and chemokine production, as well as act directly on neurons to promote neuronal injury and apoptosis. TNF-α, which is produced by both activated macrophages and astrocytes, can impair astrocyte uptake of excess glutamate and is directly neurotoxic. Additional glutamate allows excess influx of Ca^{2+}, triggering a variety of potentially harmful enzymes, as well as formation of free radicals and additional release of glutamate. This release subsequently over stimulates NMDA receptors on neighbouring neurons, initiating further injury. Abbreviations: AA, arachidonic acid; CNS, central nervous system; HIV-D, human immunodeficiency virus type 1 (HIV-1)-associated dementia; ICAM, intercellular cell adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP, monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; MIP, macrophage inflammatory protein; NMDA, *N*-methyl-D-aspartate; RANTES, 'regulated on activation, normal T-cell expressed and secreted'; SDF, stromal-cell-derived factor; TNF, tumour necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; QA, quinolinic acid; VCAM, vascular cell adhesion molecule.

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contribute to neuronal injury indirectly by further augmenting cytokine and chemokine expression or inducing expression of mononuclear phagocyte metabolites that are themselves neurotoxic. IL-1β, for example, can act on mononuclear phagocytes in an autocrine and paracrine manner to promote expression of IL-6, TNF-α, nitric oxide (NO) and L-cysteine (Refs 96, 114, 115, 116). Both TNF-α and IL-6 appear to stimulate HIV-1 replication by inducing expression of nuclear factors that are able to act on the HIV-1 long terminal repeat (LTR), including nuclear factor kappa B (NF-κB) (Ref. 117) and CCAAT/enhancer binding protein beta [C/EBPβ; also known as nuclear factor IL-6 or liver activating protein (LAP)] (Ref. 118), respectively. TNF-α might also play a role in CNS viral entry by opening a paracellular route, which allows movement through the intercellular spaces between neighbouring endothelial cells (Ref. 119).

In addition to being directly neurotoxic, TNF-α can also be neuroprotective (Refs 120, 121, 122, 123, 124). This protective feature appears to be mediated through the action of kinases and NF-κB (Refs 121, 123). Interestingly, however, long-term treatment of rat hippocampal neurons with TNF-α has been demonstrated to increase Ca^{2+} current density through NF-κB activation (Ref. 125). This might suggest that the neurotoxic character of TNF-α observed in HIV-D involves long-term modulation of voltage-dependent Ca^{2+} channels by NF-κB resulting from chronic immune dysregulation. Additionally, treatment of human fetal brain cell cultures with TNF-α and IL-1β synergistically mediates neuronal injury through involvement of NMDA receptor stimulation and NO production (Ref. 126). These results suggest a potential role for other cytokines in mediating TNF-α neurotoxicity.

TRAIL, a member of the TNF-α family, can rapidly induce apoptosis (Ref. 127). This protein is increased in human monocyte-derived macrophages after HIV-1 infection and immune activation (Ref. 128) and might contribute to the neuronal loss seen in HIV-D. In a mouse model of HIV-1 CNS infection, apoptotic neurons were generally seen in the vicinity of TRAIL-expressing mononuclear phagocytes (Ref. 129). Interestingly, TRAIL production was seen preferentially in HIV-1-infected mononuclear phagocytes, in contrast to TNF-α or IL-1β, which were expressed independently of HIV-1 infection. Neutralising antibodies against TRAIL, but not TNF-α or Fas ligand, prevented neuronal apoptosis, underscoring the significance of TRAIL in promoting HIV-D (Ref. 129).

M-CSF, a TNF-α-inducible cytokine (Ref. 130), is detectable in the CSF of HIV-1-infected adults and children (Refs 131, 132). Infected mononuclear phagocytes produce high levels of M-CSF, and mononuclear phagocytes cultured in media containing M-CSF are more susceptible to HIV-1 infection (Ref. 133). This increased susceptibility might be due, at least in part, to the ability of M-CSF to up-regulate both CD4 and CCR5 cell surface receptors (Refs 134, 135). Antagonists to M-CSF were able to inhibit HIV-1 replication in monocyte-derived macrophages, suggesting that other factors upregulated by M-CSF (e.g. transcription factors) might be involved (Ref. 136). Because M-CSF stimulates the proliferation, differentiation and survival of cells of the macrophage lineage in adults (see Ref. 137 for review), overexpression of this cytokine might add to the pool of total monocytes/macrophages by inducing proliferation and differentiation of mononuclear phagocyte progenitor cells. Also, M-CSF might contribute to the long-term survival of HIV-1-infected macrophages, providing a cellular reservoir for HIV-1 replication. In support of this hypothesis, virus replication and M-CSF production slowly return to baseline levels after introduction of azidothymidine (AZT) or ritonavir, suggesting that viral replication and M-CSF production continue well after therapy is initiated (Ref. 138).

Chemokines

Activated/stimulated mononuclear phagocytes secrete chemokines, which have also been found to be elevated in the CSF of patients with HIV-D. Their contribution to neuropathogenesis, however, is still unclear. Chemokines generally function to recruit leukocytes to areas of inflammation. Presumably, chemokine overexpression would result in excess infiltration of activated leukocytes into the CNS, leading to neuronal injury and death. Interestingly, however, the β-chemokines RANTES ('regulated on activation, normal T-cell expressed and secreted') and macrophage inflammatory protein 1β (MIP-1β), which are produced by cytotoxic T cells and function to recruit and/or activate macrophages, are elevated in the CSF of patients with HIV-D (Ref. 139), yet patients with greater CSF levels of these chemokines scored higher on neuropsychological testing than those with low or undetectable levels (Ref. 140).

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RANTES and MIP-1β, which are natural ligands of CCR5, suppress HIV-1 infection in mononuclear phagocytes (Ref. 141) and protect neurons from HIV-1 gp120-induced apoptosis in a mixed culture system (Ref. 142). The neuroprotective properties of RANTES and MIP-1β against the effects of gp120 are probably indirect, through competition with the virus for the CCR5 receptors on mononuclear phagocytes and, possibly, neurons. This is supported by the finding that the α-chemokines stromal-cell-derived factor (SDF)-1α and -1β, which are natural ligands of CXCR4 receptors, were unable to impede gp120 neurotoxicity (Ref. 142). Furthermore, in contrast to the β-chemokines, SDF-1 might contribute directly to CNS injury. N-terminal processing of SDF-1 by active matrix metalloproteinase 2 (MMP-2) (Ref. 143), which is secreted by HIV-1-infected macrophages, reportedly converts SDF-1 into a highly neurotoxic protein (Ref. 144).

Other soluble factors

Other soluble by-products of HIV-1-infected and/or activated mononuclear phagocytes also contribute to neuronal injury and apoptosis in HIV-D, including L-cysteine (Ref. 96), quinolinic acid and the neurotoxic amine NTox (Ref. 145). The neurotoxic effect of L-cysteine is mediated through excitation of the NMDA receptor (Ref. 146). TNF-α and IL-1β have been demonstrated in vitro to induce the release of L-cysteine from human monocyte-derived macrophages in a dose-dependent manner (Ref. 96). Interestingly, when infected with HIV-1, these cells produced significantly less L-cysteine than uninfected cells stimulated with TNF-α (Ref. 96).

Quinolinic acid, a tryptophan metabolite, is modestly increased in the CSF of patients with HIVE and has been found to correlate significantly with the degree of neurocognitive dysfunction (Ref. 147). In addition, a separate study found that quinolinic acid levels correlated primarily with virus levels in CSF and to a lesser extent in plasma (Ref. 148). The population in this study had a low incidence of HIV-D, which most likely account for the lack of correlation with neurocognitive dysfunction observed. This excitotoxin can produce 'axon-sparing' neuronal injury (in which the cell body is damaged but the axons remain intact) (Ref. 149) specifically through stimulation of NMDA receptors (Ref. 150). Activated mononuclear phagocytes rapidly convert L-tryptophan into quinolinic acid in CNS inflammatory diseases (Ref. 151). Using a SIVE model, investigators were able to determine that most, if not all, quinolinic acid was synthesised within the brain (Ref. 152). Presumably, the quinolinic acid is synthesised by activated mononuclear phagocytes, rather than entering the CNS from the meninges or blood. Like quinolinic acid, minute quantities of NTox can induce neuronal damage (Ref. 153).

Stimulated brain macrophages can be induced to synthesise an isoform of NO synthase, inducible NO synthase (iNOS) (Refs 154, 155). This molecule, which is increased in autopsy brain tissue of patients with HIV-D (Ref. 105) and correlates with the degree of neurocognitive dysfunction (Ref. 156), can react with superoxides to form the neurotoxin peroxynitrite (Ref. 157). Peroxynitrite stimulates a sustained increase in intracellular Ca^{2+} ions, resulting in neuronal apoptosis (Ref. 158). Levels of iNOS associate with the degree of detection of the HIV-1 coat protein gp41 (Ref. 156), suggesting a role for this envelope protein in possible immune activation and subsequent iNOS expression by stimulated mononuclear phagocytes. HIV-1 gp41 has been demonstrated in mixed rat neuronal and glial cell cultures to promote iNOS expression and induce neuronal cell death through an NO-dependent process (Ref. 159). In addition to viral-protein-induced iNOS production, immune stimulation contributes to the pool of iNOS in the brains of patients with HIV-D. Chemokine and cytokine signalling in stimulated microglia promotes p38 mitogen-activated protein kinase (MAPK) activity. Activation of this kinase results in phosphorylation/activation of the transcription factor MEF2C, which stimulates TNF-α and iNOS expression (Ref. 160).

Arachidonic acid has also been demonstrated to be increased in HIV-D and to contribute to neuropathogenesis (Ref. 161). A metabolite of arachidonate, platelet-activating factor (PAF), is rapidly produced by mononuclear phagocytes when stimulated by pathogens, including HIV-1 (Ref. 162). It is detected at high levels in the CSF of patients with HIV-D (Refs 108, 163) and correlates with cytokine activity (Ref. 108). PAF functions to activate neutrophils, eosinophils and platelets, and attract leukocytes to areas of infection (see Ref. 164 for review). In the CNS, PAF can mediate glutamate release and transcriptional activation. Neurons can also be induced to produce PAF by glutamate, which can result in

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pronounced microglial chemotaxis to the area of producing neurons (Ref. 165). This recruitment of activated mononuclear phagocytes would presumably bring more neurotoxins into the immediate vicinity of neurons, potentially contributing to neuronal injury.

Role of viral proteins in promoting neuronal injury

Shed viral proteins, apart from the complete virion, have also been demonstrated to contribute significantly to promoting neuronal injury and/or death. In vivo studies have demonstrated the ability of soluble HIV-1 Tat to generate tissue loss when injected stereotaxically in the striatum of adult rats (Ref. 166). This loss might be due to the ability of Tat to stimulate and promote a pro-inflammatory response in mononuclear phagocytes and astrocytes. Tat treatment of primary monocytes results in the rapid production of several cytokines in vitro, including transforming growth factor β (TGF-β) (Ref. 167), IL-1β, TNF-α and IL-6 (Refs 168, 169). Additionally, Tat decreases glutamate uptake by astrocytes (Ref. 94), indicating a direct role for Tat in astrocyte dysfunction. Tat also has homology to β-chemokines and has chemotactic activity (Refs 170, 171).

HIV-D is associated with an increase in the number of total brain macrophages (Ref. 58). Tat might aid in CNS invasion by mononuclear phagocytes by enhancing the chemotactic and invasive phenotype of monocytes from the peripheral blood through a number of different mechanisms. Soluble Tat treatment of primary monocytes results in increased expression of the β2 integrins, thus increasing monocyte/endothelium adhesion, and MMP-9 (Ref. 172), reportedly through Tat-induced monocyte production of IL-1β and TNF-α (Ref. 169). Tat also induces astrocytic expression of the β-chemokine MCP-1 (Refs 173, 174). Secreted MCP-1 may recruit additional monocytes/macrophages into the brain, where they subsequently release chemokines and cytokines and contribute to excess glutamate in the CNS compartment. In support of this hypothesis, SIV CSF levels of MCP-1 were reported to precede and predict SIVE (Ref. 175). Interestingly, $CD14^+CD16^+$ monocytes have been shown by flow cytometry to express MCP-1, which might contribute to a more invasive phenotype (Refs 56, 176). The importance of this characteristic is further supported by a study reported by Gonzalez et al., which demonstrated that HIV-1-infected individuals homozygous for the MCP-1 –2578G allele had a 4.5-fold increased risk of developing HIV-D (Ref. 177). This polymorphism results in increased MCP-1 expression in response to an inflammatory stimulus (Ref. 178). In response to HAART treatment, MCP-1 levels were decreased in both CSF and plasma (Ref. 179), supporting the role of virus replication and immune activation promoting MCP-1 production in the context of HIV-D. In addition to MCP-1, Tat is a potent inducer of the chemokines IL-8 and CXCL10/interferon (IFN)-γ inducible protein (IP)-10 in astrocytes (Ref. 174), presumably contributing to BBB instability and leukocyte infiltration into the CNS.

HIV-1 gp120 might contribute to HIV-D through binding of CD4 and/or the α- or β-chemokine receptors, CXCR4 and CCR5, present on mononuclear phagocytes, astrocytes and neurons. Binding of these receptors by gp120 facilitates cellular entry of the virus; however, shed gp120, apart from the complete virion, can also bind these receptors and induce activation, without infection, of the bound cell. Natural and recombinant gp120 has been demonstrated to stimulate TNF-α, IL-1β, IL-6 and GM-CSF expression by monocytes in vitro (Ref. 180). This effect is abrogated by soluble CD4, providing evidence that these cytokines are released through stimulation of the CD4 receptor by gp120. Additionally, utilising the CXCR4 receptor, gp120 has been shown to directly induce apoptosis in a human neuronal cell line in a dose-dependent manner (Ref. 181). Binding of gp120 to the CXCR4 receptor, however, does not appear to be sufficient for induction of apoptosis, in that caspase-3 is only present in neurons with internalised gp120 (Ref. 182). This same study demonstrated that brain-derived neurotrophic factor was able to prevent the pro-apoptotic effect of gp120, as well as SDF-1, a natural ligand for CXCR4 also shown to promote apoptosis in neurons (Ref. 181), by downregulating CXCR4 expression, further supporting the role of CXCR4 in promoting neuronal cell death.

HIV-1 gp120 might also contribute to HIV-D through its interaction with astrocytes. In astrocytes, expression of the CXC chemokine CXCL10/IP-10, which is found to be increased in the CNS of patients with HIV-D and might function to recruit additional leukocytes into the CNS, can be induced by gp120 produced under

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the control of the glial fibrillary acidic protein promoter in a mouse model, as well as in astrocyte cultures (Ref. 183). In this study, it was shown that CXCL10/IP-10 is probably augmented by gp120 stimulation, through a mechanism independent of IFN-γ. In addition to possibly recruiting leukocytes into the CNS, CXCL10/IP-10 might contribute directly to neuronal injury. In vitro treatment of neurons with CXCL10/IP-10 increases membrane permeability and subsequent apoptosis by means of caspase-3 activation (Ref. 184).

Role of astrocytes in HIV-D

Infection of astrocytes is believed to occur by mechanisms independent of CD4 (Ref. 185). Productive infection in vivo has not been demonstrated and in vitro studies indicate nonproductive infection (Refs 186, 187) or demonstrate only minimal quantities of virus (Refs 188, 189, 190). The abortive viral infection in astrocytes appears to result from a cellular block in Rev function that prevents nuclear localisation of Rev necessary for post-transcriptional regulation of HIV-1 expression (Ref. 188). Regardless of this fact, viral regulatory proteins and/or the action of HIV-1 infection of astrocytes might stimulate, and thus contribute to the enhanced activation status of, astrocytes.

Astrocytes are essential for uptake of excess extracellular glutamate in the CNS, thereby preventing glutamate neurotoxicity (Ref. 191). The contribution to HIV-D neuropathogenesis by astrocytes is believed to occur primarily through the release of glutamate and/or the failure to take up excess glutamate in the environment, leading to over stimulation of NMDA receptors and subsequent neuronal damage and/or loss. This loss of neuroprotection can occur through stimulation of astrocytes by viral proteins and/or cytokines and chemokines released by neighbouring mononuclear phagocytes or other astrocytes.

The chemokine SDF-1, for example, is significantly increased by astrocytes and neurons in HIV-D (Ref. 192). SDF-1 induces the extracellular release of TNF-α from astrocytes (Ref. 193). TNF-α, which is also produced by activated mononuclear phagocytes, inhibits the ability of astrocytes to take up excess glutamate (Ref. 194). Additionally, astrocyte exposure to TNF-α, IL-1β, IFN-γ or gp120 results in alterations of ion transport, specifically through stimulating Na^+–H^+ exchange (Ref. 195). This might result in an increase in intracellular pH, consequently altering astrocyte membrane permeability and enhancing glutamate efflux. TNF-α might also contribute to glutamate release by promoting astrocyte formation of the lipid mediator prostaglandin (Ref. 193), which mediates glutamate release through a Ca^{2+}-dependent mechanism (Ref. 196). In addition to cytokines and chemokines, activated mononuclear phagocytes release arachidonate and reactive oxygen species, which also impair astrocyte clearing of glutamate (Refs 161, 197, 198).

Astrocytes might also augment the effects of infected and/or stimulated mononuclear phagocytes through the actions of soluble factors produced by the mononuclear phagocytes acting on nearby astrocytes. HIV-1 infection or gp120 stimulation of mononuclear phagocytes enhances production of the pro-inflammatory cytokine IL-1β (Refs 180, 199), which can promote astrocytosis (Ref. 200). Astrocytes treated with IL-1β have been demonstrated to produce iNOS, with even greater production observed when they are co-cultured with TNF-α or IFN-γ (Ref. 201), thus adding to the pool of this neurotoxin in the CNS. In addition, astrocytes contribute to the structural integrity of the BBB and can be induced to express VCAM-1 and intercellular cell adhesion molecule (ICAM)-1 in response to cytokines, including TNF-α, IL-1β, and IFN-γ (Ref. 202), as well as HIV-1 Tat (Ref. 203), potentially contributing to the influx of mononuclear phagocytes.

Nuclear factors in HIV-D neuropathogenesis

C/EBP proteins and cytokine dysregulation

Initial cytokine dysregulation in HIV-1-infected mononuclear phagocytes might be mediated by CCAAT/enhancer binding proteins (C/EBPs), a family of transcription factors that include C/EBPα, -β, -γ, -δ, -ε and -ζ. These transcription factors are involved in myeloid cell stimulation, regulation and differentiation (see Ref. 204 for review). In unstimulated mononuclear phagocytes, C/EBPβ is fully active without requiring post-translational modification and is poised to stimulate transcription in conjunction with other factors whose activities are induced (Ref. 205).

In the setting of HIV-1 infection and AIDS, stimulation of mononuclear phagocytes through cytokines and other immune-stimulating factors might potentially induce greater production of

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C/EBPβ, generating a positive-feedback loop and resulting in overproduction of this nuclear factor. Furthermore, increased C/EBPβ production caused by inflammation and cytokine dysregulation might contribute to the activated mononuclear phagocyte phenotype observed in HIV-1/AIDS and HIV-D. For example, C/EBPβ contributes to the induction of numerous pro-inflammatory genes in mononuclear phagocytes, including cytokines found to be elevated in HIV-D (IL-1, IL-6 and TNF-α) (Ref. 206). This pro-inflammatory environment might, at least in part, account for the excess C/EBPβ expression observed in HIV-1 infected individuals (Ref. 207). Furthermore, excess C/EBPβ might contribute to cell susceptibility to HIV-1 infection by facilitating virus infectivity through increased expression of CCR5. This receptor contains several C/EBPβ-binding sites in its promoter (Ref. 207). In addition, C/EBPβ sites have been identified in the RANTES promoter (Ref. 208) and might contribute to chemotaxis through upregulation of this chemokine. C/EBP promoter regions are also involved in regulation of CD14 gene expression and are important for the synergistic signalling from TGF-β to induce monocyte differentiation (Ref. 209).

Other factors associated with the development of HIV-D also affect and/or are affected by C/EBPβ activity. PAF and lipopolysaccharide stimulation has been shown to promote a sustained increase in C/EBPβ expression (Ref. 210), thus adding to a pro-inflammatory cytokine environment. In addition, HIV-1 Tat has been demonstrated to enhance IL-6 expression through its ability to complex with C/EBPβ (Ref. 211). Tat has also been shown to induce iNOS expression by astrocytes through a mechanism involving C/EBPβ (Ref. 212).

Transcription factors and HIV-1 expression

In addition to their contribution to cytokine dysregulation in AIDS, C/EBP proteins and binding sites might also be important in viral expression. Macrophage-specific (M-tropic) virus, which predominates during initial infection and again in AIDS, utilises C/EBP proteins and sites for HIV-1 replication (Refs 213, 214). Interestingly, C/EBP LTR sites are necessary for productive viral infection in mononuclear phagocytes, but not in $CD4^+$ T cells (Ref. 213). In particular, C/EBPβ might play a key role in promoting HIV-1 transcription in mononuclear phagocytes. C/EBPβ-mediated transcription of the LTR by many HIV-1 variants has been previously reported (Ref. 215). Interestingly, in addition to increasing the susceptibility of cells to HIV-1 infection (as discussed previously), M-CSF might also contribute to the ability of the virus to replicate. M-CSF-induced macrophages produce a large amount of HIV-1, as well as haematopoietic cell kinase (Hck) and C/EBPβ (Ref. 216). In this same study, it was demonstrated that antisense suppression of Hck inhibits HIV-1 replication, possibly through increased production of the short isoform of C/EBPβ, which inhibits the transcriptional activity of C/EBPβ.

In HIV-D, sequence variation in two C/EBP sites in the HIV-1 LTR has recently been shown to correlate with disease progression (Refs 217, 218). These studies have demonstrated that LTRs derived from peripheral PBMCs with a C to T mutation in position 3 (3T) of C/EBP site I, as compared with the consensus C/EBP site I derived from clade B variants, increased significantly with concomitant immunodeficiency and severity of HIV-D (Refs 217, 218) Moreover, this phenomenon was observed in CNS-derived LTRs of several individuals with HIV-D, whereas it was absent in HIV-1-infected individuals without HIV-D. Although this C/EBP site variation leads to lower C/EBPβ affinity, it has a high affinity for HIV-1 viral protein R (Vpr) (Refs 219, 220). Vpr is a 14 kDa virion-associated protein that transactivates the HIV-1 LTR and is important for transcription of unintegrated virus. By contrast to C/EBP site I, two variants at C/EBP site II were demonstrated to be increased in the CNS of individuals with HIV-D, but decreased in PBMCs (Ref. 218). These variations might increase the activity on the LTR by C/EBPβ, as they have been shown to increase the affinity of the LTR to this factor. These findings might suggest that the virus evolves as a protected reservoir in the CNS, which can lead to a viral phenotype that promotes the development of HIV-D. Alternatively, these sequence variations could promote accumulation of a latent reservoir in PBMCs, only to be activated later by inflammatory conditions (i.e. overexpression of IL-6 and/or TNF-α), promoting reactivation and invasion of the CNS, as well as other tissues.

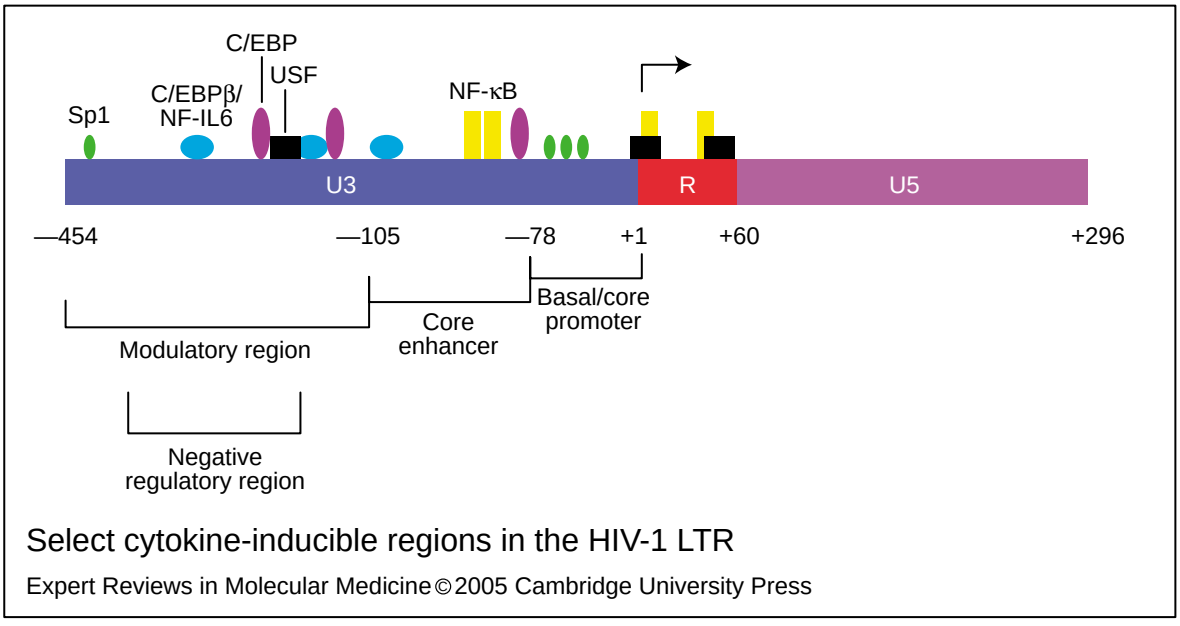
In addition to C/EBPβ, other cytokine-induced nuclear factors that also act on the virus LTR might promote expression of latent virus in activated monocyte/macrophages in HIV-D. Several cellular transcription factors upregulated during pro-inflammatory conditions have been demonstrated to bind to sequences within the LTR

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and regulate HIV-1 transcription (Fig. 2). For example, stimulatory protein 1 (Sp1) increases RNA synthesis 5–8-fold in reconstituted reactions in vitro (Ref. 221). Three tandem Sp1 sites found between nucleotides –46 to –78 of the U3 region are vital to HIV-1 production (Ref. 222), whereas a fourth site at the extreme 5' end is essential for negative-sense transcription (Ref. 223). Several cytokines, including TGF-β, have been shown to increase Sp1-mediated promoter activity (Ref. 224). TNF-α also enhances LTR activity, presumably through activation of NF-κB (Ref. 225). Like Sp1, two tandem NF-κB sites located within the U3 basal/core promoter have been identified as key to production of virus (Ref. 222). NF-κB sites might also be important in M-CSF-induced HIV-1 expression (Ref. 226). Interestingly, in DNA-binding and functional assays, C/EBPβ has been demonstrated to regulate viral gene expression independent of C/EBPβ sites in activated mononuclear phagocytes, possibly through functional interactions between C/EBPβ, upstream stimulating factor (USF) and/or NF-κB (Ref. 227).

Although beyond the scope of this review, numerous other sites located within the LTR have been reported to regulate positive and/or negative viral gene transcription through various pathways. Although the LTR does not affect the infectivity of the virus, the number and orientation of specific LTR sequences might confer cellular tropism by restricting or promoting LTR activity in a cell-specific manner. This activity is, in all likelihood, greatly influenced by the extracellular environment, resulting in a viral reservoir that is cytokine-dependent and cell-type specific, rather than organ specific. In support of this hypothesis, a recent study has found a correlation between circulating proviral HIV-1 DNA and HIV-D that remained significant even among individuals with an undetectable viral load (Ref. 228). Interestingly, preliminary analysis revealed that $CD14^{+}CD16^{+}$ monocytes, rather than T cells, carry the highest viral burden. These findings underscore the role of activated monocytes/macrophages in viral persistence and the contribution of these cells to the development of HIV-D.



Select cytokine-inducible regions in the HIV-1 LTR

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Figure 2. Select cytokine-inducible regions in the HIV-1 LTR. Binding sites within the HIV-1 long terminal repeat (LTR) for specific transcription factors are shown. In macrophages, cytokine-induced transcription factor binding might enhance virus replication under unconstrained pro-inflammatory conditions. Although having no effect on the ability of the virus to infect cells, the extracellular cytokine environment may confer cellular tropism (the ability of the virus to replicate in specific cells) by restricting or promoting LTR activity in a cell-specific manner. Abbreviations: C/EBP, CCAAT/enhancer binding protein; NF-IL6, nuclear factor IL-6; NF-κB, nuclear factor kappa B; R, transcription regulatory region; Sp1, stimulatory protein 1 (Sp1); U3, 3' untranslated region; U5, 5' untranslated region; USF, upstream stimulating factor.

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Other markers of HIV-D: the Alzheimer's disease connection

A recent study examining amyloid precursor protein (APP) in subjects with HIV-1-associated cognitive impairment found high level expression of this antigen in $CD14^+CD16^+$ cells (Ref. 229). It is interesting to note a connection between Alzheimer's disease and HIV-D with respect to the increased risk of both diseases with the apoE4/4 polymorphism (Refs 230, 231). ApoE4 influences the monocytic phenotype and normal persons homozygous for the apoE4 allele have increased CD16 expression (Ref. 232) in response to M-CSF (Ref. 233). It is conceivable that in HIV-1 infection, the apoE4 polymorphism confers an increased sensitivity to M-CSF. This cytokine, which is produced in macrophages in response to HIV-1 infection, increases monocyte/macrophage infection (Ref. 234), is produced in the CNS in HIV-1-infected individuals (Ref. 131) and has been proposed to play an important role in the pathogenesis of HIVE via activation of the monocyte/macrophage phenotype (Ref. 52). Additionally, a recent paper demonstrates that Tat inhibits the apoE-degrading enzyme neprilysin (Ref. 235), providing additional considerations for the role of viral infection with respect to apoE polymorphism, aging and HIV-D.

Therapeutic perspectives

It appears that the major reservoirs of active HIV-1 infection in the CNS are perivascular macrophages and resident microglia (Ref. 59). The increased numbers of ramified microglia in HIV-D without evidence for proliferation in brain (Ref. 64) suggests CNS invasion of mononuclear phagocytes and CNS engraftment as a major mechanism involved in the pathogenesis of the disease. While the half-life of the perivascular macrophage is normally short, they may be retained for a longer period in HIV-D and some may further enter the CNS parenchyma and take on microglial characteristics. Alternatively a different subset may give rise to parenchymal microglia. In any case, it would appear that strategies designed to abrogate virus replication in the periphery would have a beneficial effect in reducing CNS accumulation of activated and/or infected mononuclear phagocytes. The antiretroviral drugs normally have suboptimal penetrance into the CNS. A recent study in macaques infected with SIV suggests that minocycline, an antibiotic with properties enabling it to cross the BBB, has demonstrated efficacy in reducing CNS viral loads and CNS inflammation (Ref. 236). It is worth noting that in addition to its anti-inflammatory properties, minocycline also inhibited HIV/SIV replication in macrophages (Ref. 236). The combination of HAART and minocycline might be particularly effective in treating and/or preventing HIV-1-induced CNS disorders or other end-organ diseases associated with macrophage invasion in HIV-1 infection.

Therapies designed to directly abrogate neuronal excitotoxicity might also prove to be advantageous. CXCR4 has been demonstrated to mediate the neurotoxic effects of gp120 (Ref. 181) and, as such, therapeutic strategies aimed at reducing neuronal CXCR4 expression might be beneficial. NMDA receptor antagonists might also prove to be helpful. Both in vitro and in vivo studies have shown that memantine, an NMDA receptor antagonist, can prevent neuronal apoptosis after exposure to HIV-1 gp120 (Refs 237, 238), and in an HIVE mouse model, memantine significantly improved hippocampal synaptic function (Ref. 239). Interestingly, a very recent report demonstrated the ability of MK-801, a noncompetitive NMDA receptor antagonist, to also prevent microglial activation by LPS and HIV-1 Tat (Ref. 240). Given the profound contribution by brain macrophages to neuronal injury and apoptosis, this newly discovered property of MK-801 might make it a particularly useful therapy for HIV-1-associated neurocognitive disorders. Other therapeutic strategies that reduce inflammation and cytokine dysregulation or promote neuronal survival (i.e. neurotrophins) might also be beneficial (Ref. 241).

Concluding remarks

Although we discuss two means for virus entry and persistence in the CNS, we do not believe that these models are necessarily mutually exclusive of one another. Although HIV-1 infection is required for the development of HIV-D, it does not seem to be sufficient for the development of CNS disease. Rather, in addition to infection, a pro-inflammatory environment, presumably resulting from chronic immune dysregulation, appears to be necessary. Many studies suggest that the pro-inflammatory cytokine profile might promote the development of a vicious cycle of virus production and pro-inflammation, resulting in the activation of monocytes/macrophages in

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the peripheral blood. These activated cells may be more invasive and able to enter the CNS compartment, secreting factors that act to stimulate other neuroglia and advancing CNS inflammation. In addition to other by-products of inflammation, these factors are directly or indirectly neurotoxic, predominantly through over stimulation of NMDA receptors, leading to axonal injury and/or neuronal apoptosis. As such, many therapeutic strategies have been aimed at preventing or reducing the activity on the NMDA receptors (see Ref. 242 for review). An increased understanding of the mechanism(s) and kinetics of mononuclear phagocyte activation, trafficking and accumulation in the CNS is needed in order to develop therapeutics designed to prevent subsequent injury to the CNS and the development of CNS disease.

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References

1 Sacktor, N. et al. (2001) HIV-associated neurologic disease incidence changes:: Multicenter AIDS Cohort Study, 1990-1998. Neurology 56, 257-260, PubMed: 11160967
2 McArthur, J.C. et al. (1993) Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. Neurology 43, 2245-2252, PubMed: 8232937
3 Davis, L.E. et al. (1992) Early viral brain invasion in iatrogenic human immunodeficiency virus infection. Neurology 42, 1736-1739, PubMed: 1513462
4 Bell, J.E. et al. (1993) Human immunodeficiency virus and the brain: investigation of virus load and neuropathologic changes in pre-AIDS subjects. J Infect Dis 168, 818-824, PubMed: 8376829
5 Vazeux, R. et al. (1992) Low levels of human immunodeficiency virus replication in the brain tissue of children with severe acquired immunodeficiency syndrome encephalopathy. Am J Pathol 140, 137-144, PubMed: 1731520
6 Unger, E.R. et al. (1993) Male donor-derived cells in the brains of female sex-mismatched bone marrow transplant recipients: a Y-chromosome specific in situ hybridization study. J Neuropathol Exp Neurol 52, 460-470, PubMed: 8103085
7 Hickey, W.F. and Kimura, H. (1988) Perivascular microglial cells of the CNS are bone marrow-derived and present antigen in vivo. Science 239, 290-292, PubMed: 3276004
8 Williams, K., Alvarez, X. and Lackner, A.A. (2001) Central nervous system perivascular cells are immunoregulatory cells that connect the CNS with the peripheral immune system. Glia 36, 156-164, PubMed: 11596124
9 Rostad, S.W. et al. (1987) Human immunodeficiency virus (HIV) infection in brains with AIDS-related leukoencephalopathy. AIDS Res Hum Retroviruses 3, 363-373, PubMed: 3447627
10 Pumarola-Sune, T. et al. (1987) HIV antigen in the brains of patients with the AIDS dementia complex. Ann Neurol 21, 490-496, PubMed: 3296948
11 Kure, K. et al. (1991) Human immunodeficiency virus-1 infection of the nervous system: an autopsy study of 268 adult, pediatric, and fetal brains. Hum Pathol 22, 700-710, PubMed: 2071114
12 Porwit, A. et al. (1989) Cell association of HIV in AIDS-related encephalopathy and dementia. Apmis 97, 79-90, PubMed: 2914109
13 Kaul, M., Garden, G.A. and Lipton, S.A. (2001) Pathways to neuronal injury and apoptosis in HIV-associated dementia. Nature 410, 988-994, PubMed: 11309629
14 Gonzalez-Scarano, F. and Martin-Garcia, J. (2005) The neuropathogenesis of AIDS. Nat Rev Immunol 5, 69-81, PubMed: 15630430
15 Aylward, E.H. et al. (1993) Reduced basal ganglia volume in HIV-1-associated dementia: results from quantitative neuroimaging. Neurology 43, 2099-2104, PubMed: 8413973
16 Aylward, E.H. et al. (1995) Magnetic resonance imaging measurement of gray matter volume reductions in HIV dementia. Am J Psychiatry 152, 987-994, PubMed: 7793469
17 Budka, H. et al. (1987) Brain pathology induced by infection with the human immunodeficiency virus (HIV). A histological, immunocytochemical, and electron microscopical study of 100 autopsy cases. Acta Neuropathol (Berl) 75, 185-198, PubMed: 3434225
18 (1996) New drugs for HIV infection. Med Lett Drugs Ther 38, 35-37, PubMed: 8606677
19 Neuenburg, J.K. et al. (2002) HIV-related neuropathology, 1985 to 1999: rising prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy. J Acquir Immune Defic

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https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

Syndr 31, 171-177, PubMed: 12394795
20 McArthur, J.C. (2004) HIV dementia: an evolving disease. J Neuroimmunol 157, 3-10, PubMed: 15579274
21 Haggerty, S. and Stevenson, M. (1991) Predominance of distinct viral genotypes in brain and lymph node compartments of HIV-1-infected individuals. Viral Immunol 4, 123-131, PubMed: 1684709
22 Enting, R.H. et al. (1998) Antiretroviral drugs and the central nervous system. Aids 12, 1941-1955, PubMed: 9814862
23 Brodt, H.R. et al. (1997) Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. Aids 11, 1731-1738, PubMed: 9386808
24 Dore, G.J. et al. (1999) Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. Aids 13, 1249-1253, PubMed: 10416530
25 Chiriboga, C.A. et al. (2005) Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active antiretroviral therapy (HAART). J Pediatr 146, 402-407, PubMed: 15756229
26 Bell, J.E. (2004) An update on the neuropathology of HIV in the HAART era. Histopathology 45, 549-559, PubMed: 15569045
27 Moses, A.V. et al. (1993) Human immunodeficiency virus infection of human brain capillary endothelial cells occurs via a CD4/galactosylceramide-independent mechanism. Proc Natl Acad Sci U S A 90, 10474-10478, PubMed: 7504264
28 Wiley, C.A. et al. (1986) Cellular localization of human immunodeficiency virus infection within the brains of acquired immune deficiency syndrome patients. Proc Natl Acad Sci U S A 83, 7089-7093, PubMed: 3018755
29 Chen, H., Wood, C. and Petito, C.K. (2000) Comparisons of HIV-1 viral sequences in brain, choroid plexus and spleen: potential role of choroid plexus in the pathogenesis of HIV encephalitis. J Neurovirol 6, 498-506, PubMed: 11175322
30 Harouse, J.M. et al. (1989) Human choroid plexus cells can be latently infected with human immunodeficiency virus. Ann Neurol 25, 406-411, PubMed: 2653176
31 Meltzer, M.S. et al. (1990) Role of mononuclear phagocytes in the pathogenesis of human immunodeficiency virus infection. Annu Rev Immunol 8, 169-194, PubMed: 2188662
32 Poluektova, L.Y. et al. (2002) Generation of cytotoxic T cells against virus-infected human brain macrophages in a murine model of HIV-1 encephalitis. J Immunol 168, 3941-3949, PubMed: 11937550
33 von Giesen, H.J. et al. (2005) Cerebrospinal fluid HIV viral load in different phases of HIV-associated brain disease. J Neurol 252, 801-807, PubMed: 15750706
34 McArthur, J.C. et al. (1997) Relationship between human immunodeficiency virus-associated dementia and viral load in cerebrospinal fluid and brain. Ann Neurol 42, 689-698, PubMed: 9392567
35 Cinque, P. et al. (1998) Cerebrospinal fluid HIV-1 RNA levels: correlation with HIV encephalitis. Aids 12, 389-394, PubMed: 9520168
36 Williams, K. et al. (2001) CD8 T lymphocytes control the development of SIV encephalitis: implications for the neuropathogenesis of AIDS. International Society of Neuroimmunology Sixth International Congress, J Neuroimmunol 118, Abstract 384
37 Williams, K.C. et al. (2001) Perivascular macrophages are the primary cell type productively infected by simian immunodeficiency virus in the brains of macaques: implications for the neuropathogenesis of AIDS. J Exp Med 193, 905-915, PubMed: 11304551
38 Clements, J.E. et al. (2002) The central nervous system as a reservoir for simian immunodeficiency virus (SIV): steady-state levels of SIV DNA in brain from acute through asymptomatic infection. J Infect Dis 186, 905-913, PubMed: 12232830
39 Clements, J.E. et al. (2005) The central nervous system is a viral reservoir in simian immunodeficiency virus—infected macaques on combined antiretroviral therapy: a model for human immunodeficiency virus patients on highly active antiretroviral therapy. J Neurovirol 11, 180-189, PubMed: 16036796
40 Stingele, K. et al. (2001) Independent HIV replication in paired CSF and blood viral isolates during antiretroviral therapy. Neurology 56, 355-361, PubMed: 11171901
41 Tashima, K.T. et al. (2002) Discordant Human Immunodeficiency Virus Type 1 drug resistance mutations, including K103N, observed in cerebrospinal fluid and plasma. Clin Infect Dis 35, 82-83, PubMed: 12060879
42 Strain, M.C. et al. (2005) Genetic composition of human immunodeficiency virus type 1 in

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
©2005 Cambridge University Press

https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

cerebrospinal fluid and blood without treatment and during failing antiretroviral therapy. J Virol 79, 1772-1788, PubMed: 15650202
43 Cunningham, P.H. et al. (2000) Evidence for independent development of resistance to HIV-1 reverse transcriptase inhibitors in the cerebrospinal fluid. Aids 14, 1949-1954, PubMed: 10997399
44 Ho, D.D. et al. (1995) Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373, 123-126, PubMed: 7816094
45 Wei, X. et al. (1995) Viral dynamics in human immunodeficiency virus type 1 infection. Nature 373, 117-122, PubMed: 7529365
46 Peters, P.J. et al. (2004) Biological analysis of human immunodeficiency virus type 1 R5 envelopes amplified from brain and lymph node tissues of AIDS patients with neuropathology reveals two distinct tropism phenotypes and identifies envelopes in the brain that confer an enhanced tropism and fusigenicity for macrophages. J Virol 78, 6915-6926, PubMed: 15194768
47 Liu, Y. et al. (2000) Analysis of human immunodeficiency virus type 1 gp160 sequences from a patient with HIV dementia: evidence for monocyte trafficking into brain. J Neurovirol 6 Suppl 1, S70-81, PubMed: 10871768
48 Wang, T.H. et al. (2001) Identification of shared populations of human immunodeficiency virus type 1 infecting microglia and tissue macrophages outside the central nervous system. J Virol 75, 11686-11699, PubMed: 11689650
49 Smit, T.K. et al. (2004) Independent evolution of human immunodeficiency virus (HIV) drug resistance mutations in diverse areas of the brain in HIV-infected patients, with and without dementia, on antiretroviral treatment. J Virol 78, 10133-10148, PubMed: 15331746
50 Burkala, E.J. et al. (2005) Compartmentalization of HIV-1 in the central nervous system: role of the choroid plexus. Aids 19, 675-684, PubMed: 15821393
51 Pulliam, L. et al. (1997) Unique monocyte subset in patients with AIDS dementia. Lancet 349, 692-695, PubMed: 9078201
52 Gartner, S. (2000) HIV infection and dementia. Science 287, 602-604, PubMed: 10691542
53 Passlick, B., Flieger, D. and Ziegler-Heitbrock, H.W. (1989) Identification and characterization of a novel monocyte subpopulation in human peripheral blood. Blood 74, 2527-2534, PubMed: 2478233
54 Thieblemont, N. et al. (1995) CD14lowCD16high: a cytokine-producing monocyte subset which expands during human immunodeficiency virus infection. Eur J Immunol 25, 3418-3424, PubMed: 8566032
55 Scherberich, J.E. and Nockher, W.A. (2000) Blood monocyte phenotypes and soluble endotoxin receptor CD14 in systemic inflammatory diseases and patients with chronic renal failure. Nephrol Dial Transplant 15, 574-578, PubMed: 10809793
56 Pulliam, L., Sun, B. and Rempel, H. (2004) Invasive chronic inflammatory monocyte phenotype in subjects with high HIV-1 viral load. J Neuroimmunol 157, 93-98, PubMed: 15579285
57 Sasseville, V.G. et al. (1994) Monocyte adhesion to endothelium in simian immunodeficiency virus-induced AIDS encephalitis is mediated by vascular cell adhesion molecule-1/alpha 4 beta 1 integrin interactions. Am J Pathol 144, 27-40, PubMed: 7507300
58 Glass, J.D. et al. (1995) Immunocytochemical quantitation of human immunodeficiency virus in the brain: correlations with dementia. Ann Neurol 38, 755-762, PubMed: 7486867
59 Fischer-Smith, T. et al. (2001) CNS invasion by CD14+/CD16+ peripheral blood-derived monocytes in HIV dementia: perivascular accumulation and reservoir of HIV infection. J Neurovirol 7, 528-541, PubMed: 11704885
60 Ford, A.L. et al. (1995) Normal adult ramified microglia separated from other central nervous system macrophages by flow cytometric sorting. Phenotypic differences defined and direct ex vivo antigen presentation to myelin basic protein-reactive CD4+ T cells compared. J Immunol 154, 4309-4321, PubMed: 7722289
61 Sedgwick, J.D. et al. (1993) Resident macrophages (ramified microglia) of the adult brown Norway rat central nervous system are constitutively major histocompatibility complex class II positive. J Exp Med 177, 1145-1152, PubMed: 8459208
62 Ulvestad, E. et al. (1994) Phenotypic differences between human monocytes/macrophages and microglial cells studied in situ and in vitro. J Neuropathol Exp Neurol 53, 492-501, PubMed: 8083690
63 Williams, K. et al. (1992) Biology of adult human microglia in culture: comparisons with peripheral blood monocytes and astrocytes. J Neuropathol Exp Neurol 51, 538-549, PubMed: 1517774
64 Fischer-Smith, T. et al. (2004) Macrophage/

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
©2005 Cambridge University Press

https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

microglial accumulation and proliferating cell nuclear antigen expression in the central nervous system in human immunodeficiency virus encephalopathy. Am J Pathol 164, 2089-2099, PubMed: 15161643
65 Amirayan-Chevillard, N. et al. (2000) Impact of highly active anti-retroviral therapy (HAART) on cytokine production and monocyte subsets in HIV-infected patients. Clin Exp Immunol 120, 107-112, PubMed: 10759771
66 Avison, M.J. et al. (2004) Neuroimaging correlates of HIV-associated BBB compromise. J Neuroimmunol 157, 140-146, PubMed: 15579291
67 Roberts, E.S. et al. (2003) Induction of pathogenic sets of genes in macrophages and neurons in NeuroAIDS. Am J Pathol 162, 2041-2057, PubMed: 12759259
68 Roberts, E.S., Masliah, E. and Fox, H.S. (2004) CD163 identifies a unique population of ramified microglia in HIV encephalitis (HIVE). J Neuropathol Exp Neurol 63, 1255-1264, PubMed: 15624762
69 Sulahian, T.H. et al. (2000) Human monocytes express CD163, which is upregulated by IL-10 and identical to p155. Cytokine 12, 1312-1321, PubMed: 10975989
70 [Reference deleted at proof stage.]
71 [Reference deleted at proof stage.]
72 Rezaie, P. and Male, D. (2003) Microglia in fetal and adult human brain can be distinguished from other mononuclear phagocytes through their lack of CD163 expression. Neuroembryology 2, 130-133
73 Buechler, C. et al. (2000) Regulation of scavenger receptor CD163 expression in human monocytes and macrophages by pro- and antiinflammatory stimuli. J Leukoc Biol 67, 97-103, PubMed: 10648003
74 Sidenius, N. et al. (2004) Expression of the urokinase plasminogen activator and its receptor in HIV-1-associated central nervous system disease. J Neuroimmunol 157, 133-139, PubMed: 15579290
75 Cinque, P. et al. (2004) The urokinase receptor is overexpressed in the AIDS dementia complex and other neurological manifestations. Ann Neurol 55, 687-694, PubMed: 15122709
76 Torres-Munoz, J. et al. (2001) Detection of HIV-1 gene sequences in hippocampal neurons isolated from postmortem AIDS brains by laser capture microdissection. J Neuropathol Exp Neurol 60, 885-892, PubMed: 11556545
77 Chao, C.C., Hu, S. and Peterson, P.K. (1996) Glia: the not so innocent bystanders. J Neurovirol 2, 234-239, PubMed: 8799214
78 Zheng, J. and Gendelman, H.E. (1997) The HIV-1 associated dementia complex: a metabolic encephalopathy fueled by viral replication in mononuclear phagocytes. Curr Opin Neurol 10, 319-325, PubMed: 9266156
79 Nottet, H.S. et al. (1997) Cellular aspects of HIV-1 infection of macrophages leading to neuronal dysfunction in in vitro models for HIV-1 encephalitis. J Leukoc Biol 62, 107-116, PubMed: 9226001
80 Garden, G.A. (2002) Microglia in human immunodeficiency virus-associated neurodegeneration. Glia 40, 240-251, PubMed: 12379911
81 Anderson, E. et al. (2002) HIV-1-associated dementia: a metabolic encephalopathy perpetrated by virus-infected and immune-competent mononuclear phagocytes. J Acquir Immune Defic Syndr 31 Suppl 2, S43-54, PubMed: 12394782
82 Regulier, E.G. et al. (2004) T-cell and neuronal apoptosis in HIV infection: implications for therapeutic intervention. Int Rev Immunol 23, 25-59, PubMed: 14690854
83 Peruzzi, F. et al. (2002) Tat-induced deregulation of neuronal differentiation and survival by nerve growth factor pathway. J Neurovirol 8 Suppl 2, 91-96, PubMed: 12491158
84 Bell, J.E. (1998) The neuropathology of adult HIV infection. Rev Neurol (Paris) 154, 816-829, PubMed: 9932303
85 Kaul, M. et al. (2005) HIV-1 infection and AIDS: consequences for the central nervous system. Cell Death Differ 12 Suppl 1, 878-892, PubMed: 15832177
86 Lipton, S.A. (1996) Similarity of neuronal cell injury and death in AIDS dementia and focal cerebral ischemia: potential treatment with NMDA open-channel blockers and nitric oxide-related species. Brain Pathol 6, 507-517, PubMed: 8944320
87 Lipton, S.A. (1998) Neuronal injury associated with HIV-1: approaches to treatment. Annu Rev Pharmacol Toxicol 38, 159-177, PubMed: 9597152
88 Persidsky, Y. et al. (2000) Mononuclear phagocytes mediate blood-brain barrier compromise and neuronal injury during HIV-1-associated dementia. J Leukoc Biol 68, 413-422, PubMed: 10985259
89 Ryan, L.A. et al. (2002) Macrophages, chemokines and neuronal injury in HIV-1-

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
©2005 Cambridge University Press

https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

associated dementia. Cell Mol Biol (Noisy-le-grand) 48, 137-150, PubMed: 11995633
90 Brandimarti, R. et al. (2004) Regulation of cell cycle proteins by chemokine receptors: A novel pathway in human immunodeficiency virus neuropathogenesis? J Neurovirol 10 Suppl 1, 108-112, PubMed: 14982748
91 Yi, Y. et al. (2004) Chemokine receptor utilization and macrophage signaling by human immunodeficiency virus type 1 gp120: Implications for neuropathogenesis. J Neurovirol 10 Suppl 1, 91-96, PubMed: 14982745
92 Saha, R.N. and Pahan, K. (2003) Tumor necrosis factor-alpha at the crossroads of neuronal life and death during HIV-associated dementia. J Neurochem 86, 1057-1071, PubMed: 12911614
93 Zhao, J. et al. (2004) Mitochondrial glutaminase enhances extracellular glutamate production in HIV-1-infected macrophages: linkage to HIV-1 associated dementia. J Neurochem 88, 169-180, PubMed: 14675161
94 Koller, H. et al. (2001) HIV-1 protein Tat reduces the glutamate-induced intracellular Ca2+ increase in cultured cortical astrocytes. Eur J Neurosci 14, 1793-1799, PubMed: 11860474
95 Dreyer, E.B. and Lipton, S.A. (1995) The coat protein gp120 of HIV-1 inhibits astrocyte uptake of excitatory amino acids via macrophage arachidonic acid. Eur J Neurosci 7, 2502-2507, PubMed: 8845955
96 Yeh, M.W. et al. (2000) Cytokine-stimulated, but not HIV-infected, human monocyte-derived macrophages produce neurotoxic levels of l -cysteine. J Immunol 164, 4265-4270, PubMed: 10754324
97 Shi, B. et al. (1996) Apoptosis induced by HIV-1 infection of the central nervous system. J Clin Invest 98, 1979-1990, PubMed: 8903316
98 Kolson, D.L. et al. (2004) Gene expression in TUNEL-positive neurons in human immunodeficiency virus-infected brain. J Neurovirol 10 Suppl 1, 102-107, PubMed: 14982747
99 Thompson, K.A., McArthur, J.C. and Wesselingh, S.L. (2001) Correlation between neurological progression and astrocyte apoptosis in HIV-associated dementia. Ann Neurol 49, 745-752, PubMed: 11409426
100 Adle-Biassette, H. et al. (1999) Neuronal apoptosis does not correlate with dementia in HIV infection but is related to microglial activation and axonal damage. Neuropathol Appl Neurobiol 25, 123-133, PubMed: 10216000
101 Zheng, J. et al. (2001) HIV-1 infected and immune competent mononuclear phagocytes induce quantitative alterations in neuronal dendritic arbor: relevance for HIV-1-associated dementia. Neurotox Res 3, 443-459, PubMed: 14715458
102 Gray, F. et al. (2001) Neuropathology and neurodegeneration in human immunodeficiency virus infection. Pathogenesis of HIV-induced lesions of the brain, correlations with HIV-associated disorders and modifications according to treatments. Clin Neuropathol 20, 146-155, PubMed: 11495003
103 Achim, C.L., Heyes, M.P. and Wiley, C.A. (1993) Quantitation of human immunodeficiency virus, immune activation factors, and quinolinic acid in AIDS brains. J Clin Invest 91, 2769-2775, PubMed: 8514884
104 Perrella, O. et al. (1992) Interleukin-6 and granulocyte macrophage-CSF in the cerebrospinal fluid from HIV infected subjects with involvement of the central nervous system. Arq Neuropsiquiatr 50, 180-182, PubMed: 1308387
105 Zhao, M.L. et al. (2001) Expression of inducible nitric oxide synthase, interleukin-1 and caspase-1 in HIV-1 encephalitis. J Neuroimmunol 115, 182-191, PubMed: 11282169
106 Rappaport, J. et al. (1999) Molecular pathway involved in HIV-1-induced CNS pathology: role of viral regulatory protein, Tat. J Leukoc Biol 65, 458-465, PubMed: 10204574
107 Sundar, S.K. et al. (1991) Human immunodeficiency virus glycoprotein (gp120) infused into rat brain induces interleukin 1 to elevate pituitary-adrenal activity and decrease peripheral cellular immune responses. Proc Natl Acad Sci U S A 88, 11246-11250, PubMed: 1662389
108 Genis, P. et al. (1992) Cytokines and arachidonic metabolites produced during human immunodeficiency virus (HIV)-infected macrophage-astroglia interactions: implications for the neuropathogenesis of HIV disease. J Exp Med 176, 1703-1718, PubMed: 1460427
109 Ehrenreich, H. et al. (1993) Potent stimulation of monocytic endothelin-1 production by HIV-1 glycoprotein 120. J Immunol 150, 4601-4609, PubMed: 8482849
110 Canque, B. et al. (1996) Macrophage inflammatory protein-1alpha is induced by human immunodeficiency virus infection of monocyte-derived macrophages. Blood 87, 2011-2019, PubMed: 8634452
111 Molina, J.M. et al. (1990) Production of cytokines

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
©2005 Cambridge University Press

https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

by peripheral blood monocytes/macrophages infected with human immunodeficiency virus type 1 (HIV-1). J Infect Dis 161, 888-893, PubMed: 2182729
112 Foli, A. et al. (1997) Effects of human immunodeficiency virus and colony-stimulating factors on the production of interleukin 6 and tumor necrosis factor alpha by monocyte/macrophages. AIDS Res Hum Retroviruses 13, 829-839, PubMed: 9197377
113 Talley, A.K. et al. (1995) Tumor necrosis factor alpha-induced apoptosis in human neuronal cells: protection by the antioxidant N-acetylcysteine and the genes bcl-2 and crmA. Mol Cell Biol 15, 2359-2366, PubMed: 7739519
114 Bose, M. and Farnia, P. (1995) Proinflammatory cytokines can significantly induce human mononuclear phagocytes to produce nitric oxide by a cell maturation-dependent process. Immunol Lett 48, 59-64, PubMed: 8847093
115 Granowitz, E.V. et al. (1992) Effect of interleukin-1 (IL-1) blockade on cytokine synthesis: I. IL-1 receptor antagonist inhibits IL-1-induced cytokine synthesis and blocks the binding of IL-1 to its type II receptor on human monocytes. Blood 79, 2356-2363, PubMed: 1533322
116 Tosato, G. and Jones, K.D. (1990) Interleukin-1 induces interleukin-6 production in peripheral blood monocytes. Blood 75, 1305-1310, PubMed: 2310829
117 Duh, E.J. et al. (1989) Tumor necrosis factor alpha activates human immunodeficiency virus type 1 through induction of nuclear factor binding to the NF-kappa B sites in the long terminal repeat. Proc Natl Acad Sci U S A 86, 5974-5978, PubMed: 2762307
118 Tesmer, V.M. et al. (1993) NF-IL6-mediated transcriptional activation of the long terminal repeat of the human immunodeficiency virus type 1. Proc Natl Acad Sci U S A 90, 7298-7302, PubMed: 8346247
119 Fiala, M. et al. (1997) TNF-alpha opens a paracellular route for HIV-1 invasion across the blood-brain barrier. Mol Med 3, 553-564, PubMed: 9307983
120 Suzuki, T. et al. (2004) Production and release of neuroprotective tumor necrosis factor by P2X7 receptor-activated microglia. J Neurosci 24, 1-7, PubMed: 14715932
121 Glazner, G.W. and Mattson, M.P. (2000) Differential effects of BDNF, ADNF9, and TNFalpha on levels of NMDA receptor subunits, calcium homeostasis, and neuronal vulnerability to excitotoxicity. Exp Neurol 161, 442-452, PubMed: 10686066
122 Toku, K. et al. (1998) Microglial cells prevent nitric oxide-induced neuronal apoptosis in vitro. J Neurosci Res 53, 415-425, PubMed: 9710261
123 Barger, S.W. et al. (1995) Tumor necrosis factors alpha and beta protect neurons against amyloid beta-peptide toxicity: evidence for involvement of a kappa B-binding factor and attenuation of peroxide and Ca2+ accumulation. Proc Natl Acad Sci U S A 92, 9328-9332, PubMed: 7568127
124 Cheng, B., Christakos, S. and Mattson, M.P. (1994) Tumor necrosis factors protect neurons against metabolic-excitotoxic insults and promote maintenance of calcium homeostasis. Neuron 12, 139-153, PubMed: 7507336
125 Furukawa, K. and Mattson, M.P. (1998) The transcription factor NF-kappaB mediates increases in calcium currents and decreases in NMDA- and AMPA/kainate-induced currents induced by tumor necrosis factor-alpha in hippocampal neurons. J Neurochem 70, 1876-1886, PubMed: 9572271
126 Chao, C.C. et al. (1995) Interleukin-1 and tumor necrosis factor-alpha synergistically mediate neurotoxicity: involvement of nitric oxide and of N-methyl-D-aspartate receptors. Brain Behav Immun 9, 355-365, PubMed: 8903852
127 Wiley, S.R. et al. (1995) Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity 3, 673-682, PubMed: 8777713
128 Ryan, L.A. et al. (2004) TNF-related apoptosis-inducing ligand mediates human neuronal apoptosis: links to HIV-1-associated dementia. J Neuroimmunol 148, 127-139, PubMed: 14975593
129 Miura, Y. et al. (2003) Tumor necrosis factor-related apoptosis-inducing ligand induces neuronal death in a murine model of HIV central nervous system infection. Proc Natl Acad Sci U S A 100, 2777-2782, PubMed: 12601160
130 Oster, W. et al. (1987) Tumor necrosis factor (TNF)-alpha but not TNF-beta induces secretion of colony stimulating factor for macrophages (CSF-1) by human monocytes. Blood 70, 1700-1703, PubMed: 3499192
131 Gallo, P. et al. (1994) M-CSF production by HIV-1-infected monocytes and its intrathecal synthesis. Implications for neurological HIV-1-related disease. J Neuroimmunol 51, 193-198, PubMed: 8182117
132 Gallo, P. et al. (1991) Immunological markers in the cerebrospinal fluid of HIV-1-infected

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
©2005 Cambridge University Press

https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

children. Acta Paediatr Scand 80, 659-666, PubMed: 1867084
133 Gruber, M.F. et al. (1995) Endogenous macrophage CSF production is associated with viral replication in HIV-1-infected human monocyte-derived macrophages. J Immunol 154, 5528-5535, PubMed: 7537309
134 Bergamini, A. et al. (1994) Macrophage colony-stimulating factor enhances the susceptibility of macrophages to infection by human immunodeficiency virus and reduces the activity of compounds that inhibit virus binding. Blood 84, 3405-3412, PubMed: 7524738
135 Wang, J. et al. (1998) Cytokine regulation of human immunodeficiency virus type 1 entry and replication in human monocytes/macrophages through modulation of CCR5 expression. J Virol 72, 7642-7647, PubMed: 9696868
136 Kutza, J. et al. (2000) Macrophage colony-stimulating factor antagonists inhibit replication of HIV-1 in human macrophages. J Immunol 164, 4955-4960, PubMed: 10779806
137 Pixley, F.J. and Stanley, E.R. (2004) CSF-1 regulation of the wandering macrophage: complexity in action. Trends Cell Biol 14, 628-638, PubMed: 15519852
138 Kutza, J. et al. (2002) Inhibition of HIV replication and macrophage colony-stimulating factor production in human macrophages by antiretroviral agents. AIDS Res Hum Retroviruses 18, 619-625, PubMed: 12079557
139 Kelder, W. et al. (1998) Beta-chemokines MCP-1 and RANTES are selectively increased in cerebrospinal fluid of patients with human immunodeficiency virus-associated dementia. Ann Neurol 44, 831-835, PubMed: 9818943
140 Letendre, S.L., Lanier, E.R. and McCutchan, J.A. (1999) Cerebrospinal fluid beta chemokine concentrations in neurocognitively impaired individuals infected with human immunodeficiency virus type 1. J Infect Dis 180, 310-319, PubMed: 10395844
141 Cocchi, F. et al. (1995) Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8+ T cells. Science 270, 1811-1815, PubMed: 8525373
142 Kaul, M. and Lipton, S.A. (1999) Chemokines and activated macrophages in HIV gp120-induced neuronal apoptosis. Proc Natl Acad Sci U S A 96, 8212-8216, PubMed: 10393974
143 McQuibban, G.A. et al. (2001) Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1. J Biol Chem 276, 43503-43508, PubMed: 11571304
144 Zhang, K. et al. (2003) HIV-induced metalloproteinase processing of the chemokine stromal cell derived factor-1 causes neurodegeneration. Nat Neurosci 6, 1064-1071, PubMed: 14502291
145 Giulian, D., Vaca, K. and Noonan, C.A. (1990) Secretion of neurotoxins by mononuclear phagocytes infected with HIV-1. Science 250, 1593-1596, PubMed: 2148832
146 Olney, J.W. et al. (1990) L-cysteine, a bicarbonate-sensitive endogenous excitotoxin. Science 248, 596-599, PubMed: 2185543
147 Heyes, M.P. et al. (1991) Quinolinic acid in cerebrospinal fluid and serum in HIV-1 infection: relationship to clinical and neurological status. Ann Neurol 29, 202-209, PubMed: 1826418
148 Valle, M. et al. (2004) CSF quinolinic acid levels are determined by local HIV infection: cross-sectional analysis and modelling of dynamics following antiretroviral therapy. Brain 127, 1047-1060, PubMed: 15013955
149 Schwarcz, R., Whetsell, W.O., Jr. and Mangano, R.M. (1983) Quinolinic acid: an endogenous metabolite that produces axon-sparing lesions in rat brain. Science 219, 316-318, PubMed: 6849138
150 Levivier, M. and Przedborski, S. (1998) Quinolinic acid-induced lesions of the rat striatum: quantitative autoradiographic binding assessment. Neurol Res 20, 46-56, PubMed: 9471103
151 Lane, J.H. et al. (1996) Neuroinvasion by simian immunodeficiency virus coincides with increased numbers of perivascular macrophages/microglia and intrathecal immune activation. J Neurovirol 2, 423-432, PubMed: 8972425
152 Heyes, M.P. et al. (1998) Sources of the neurotoxin quinolinic acid in the brain of HIV-1-infected patients and retrovirus-infected macaques. Faseb J 12, 881-896, PubMed: 9657528
153 Giulian, D. et al. (1996) Study of receptor-mediated neurotoxins released by HIV-1-infected mononuclear phagocytes found in human brain. J Neurosci 16, 3139-3153, PubMed: 8627353
154 Boje, K.M. and Arora, P.K. (1992) Microglial-produced nitric oxide and reactive nitrogen oxides mediate neuronal cell death. Brain Res 587, 250-256, PubMed: 1381982
155 Chao, C.C. et al. (1992) Activated microglia mediate neuronal cell injury via a nitric oxide mechanism. J Immunol 149, 2736-2741, PubMed: 1383325

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
©2005 Cambridge University Press

https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

156 Adamson, D.C. et al. (1999) Rate and severity of HIV-associated dementia (HAD): correlations with Gp41 and iNOS. Mol Med 5, 98-109, PubMed: 10203575
157 Lipton, S.A. et al. (1993) A redox-based mechanism for the neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds. Nature 364, 626-632, PubMed: 8394509
158 Leist, M. et al. (1997) Peroxynitrite and nitric oxide donors induce neuronal apoptosis by eliciting autocrine excitotoxicity. Eur J Neurosci 9, 1488-1498, PubMed: 9240406
159 Adamson, D.C. et al. (1996) Immunologic NO synthase: elevation in severe AIDS dementia and induction by HIV-1 gp41. Science 274, 1917-1921, PubMed: 8943206
160 Bhat, N.R. et al. (1998) Extracellular signal-regulated kinase and p38 subgroups of mitogen-activated protein kinases regulate inducible nitric oxide synthase and tumor necrosis factor-alpha gene expression in endotoxin-stimulated primary glial cultures. J Neurosci 18, 1633-1641, PubMed: 9464988
161 Barbour, B. et al. (1989) Arachidonic acid induces a prolonged inhibition of glutamate uptake into glial cells. Nature 342, 918-920, PubMed: 2512508
162 Gelbard, H.A. et al. (1994) Platelet-activating factor: a candidate human immunodeficiency virus type 1-induced neurotoxin. J Virol 68, 4628-4635, PubMed: 8207837
163 Heyes, M.P. et al. (1989) Cerebrospinal fluid quinolinic acid concentrations are increased in acquired immune deficiency syndrome. Ann Neurol 26, 275-277, PubMed: 2528321
164 Stafforini, D.M. et al. (2003) Platelet-activating factor, a pleiotrophic mediator of physiological and pathological processes. Crit Rev Clin Lab Sci 40, 643-672, PubMed: 14708958
165 Aihara, M. et al. (2000) Interaction between neurone and microglia mediated by platelet-activating factor. Genes Cells 5, 397-406, PubMed: 10886367
166 Bansal, A.K. et al. (2000) Neurotoxicity of HIV-1 proteins gp120 and Tat in the rat striatum. Brain Res 879, 42-49, PubMed: 11011004
167 Zauli, G. et al. (1992) tat protein stimulates production of transforming growth factor-beta 1 by marrow macrophages: a potential mechanism for human immunodeficiency virus-1-induced hematopoietic suppression. Blood 80, 3036-3043, PubMed: 1281686
168 Zauli, G. et al. (1993) Human immunodeficiency virus type 1 (HIV-1) tat-protein stimulates the production of interleukin-6 (IL-6) by peripheral blood monocytes. New Microbiol 16, 115-120, PubMed: 8510564
169 Lafrenie, R.M. et al. (1997) Activation of monocytes by HIV-Tat treatment is mediated by cytokine expression. J Immunol 159, 4077-4083, PubMed: 9378998
170 de Paulis, A. et al. (2000) Tat protein is an HIV-1-encoded beta-chemokine homolog that promotes migration and up-regulates CCR3 expression on human Fc epsilon RI+ cells. J Immunol 165, 7171-7179, PubMed: 11120849
171 Albini, A. et al. (1998) HIV-1 Tat protein mimicry of chemokines. Proc Natl Acad Sci U S A 95, 13153-13158, PubMed: 9789057
172 Lafrenie, R.M. et al. (1996) HIV-1-Tat modulates the function of monocytes and alters their interactions with microvessel endothelial cells. A mechanism of HIV pathogenesis. J Immunol 156, 1638-1645, PubMed: 8568270
173 Weiss, J.M. et al. (1999) HIV-1 Tat induces monocyte chemoattractant protein-1-mediated monocyte transmigration across a model of the human blood-brain barrier and up-regulates CCR5 expression on human monocytes. J Immunol 163, 2953-2959, PubMed: 10453044
174 Kutsch, O. et al. (2000) Induction of the chemokines interleukin-8 and IP-10 by human immunodeficiency virus type 1 tat in astrocytes. J Virol 74, 9214-9221, PubMed: 10982368
175 Zink, M.C. et al. (2001) Increased macrophage chemoattractant protein-1 in cerebrospinal fluid precedes and predicts simian immunodeficiency virus encephalitis. J Infect Dis 184, 1015-1021, PubMed: 11574916
176 Ancuta, P., Weiss, L. and Haeffner-Cavaillon, N. (2000) CD14+CD16++ cells derived in vitro from peripheral blood monocytes exhibit phenotypic and functional dendritic cell-like characteristics. Eur J Immunol 30, 1872-1883, PubMed: 10940876
177 Gonzalez, E. et al. (2002) HIV-1 infection and AIDS dementia are influenced by a mutant MCP-1 allele linked to increased monocyte infiltration of tissues and MCP-1 levels. Proc Natl Acad Sci U S A 99, 13795-13800, PubMed: 12374865
178 Rovin, B.H., Lu, L. and Saxena, R. (1999) A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. Biochem Biophys Res Commun 259, 344-348, PubMed: 10362511
179 Chang, L. et al. (2004) Antiretroviral treatment alters relationship between MCP-1 and

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https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

neurometabolites in HIV patients. Antivir Ther 9, 431-440, PubMed: 15259906
180 Clouse, K.A. et al. (1991) The HIV-1 gp120 envelope protein has the intrinsic capacity to stimulate monokine secretion. J Immunol 147, 2892-2901, PubMed: 1918997
181 Hesselgesser, J. et al. (1998) Neuronal apoptosis induced by HIV-1 gp120 and the chemokine SDF-1 alpha is mediated by the chemokine receptor CXCR4. Curr Biol 8, 595-598, PubMed: 9601645
182 Bachis, A., Major, E.O. and Mocchetti, I. (2003) Brain-derived neurotrophic factor inhibits human immunodeficiency virus-1/gp120-mediated cerebellar granule cell death by preventing gp120 internalization. J Neurosci 23, 5715-5722, PubMed: 12843275
183 Asensio, V.C. et al. (2001) Interferon-independent, human immunodeficiency virus type 1 gp120-mediated induction of CXCL10/IP-10 gene expression by astrocytes in vivo and in vitro. J Virol 75, 7067-7077, PubMed: 11435587
184 Sui, Y. et al. (2004) Neuronal apoptosis is mediated by CXCL10 overexpression in simian human immunodeficiency virus encephalitis. Am J Pathol 164, 1557-1566, PubMed: 15111302
185 Liu, Y. et al. (2004) CD4-independent infection of astrocytes by human immunodeficiency virus type 1: requirement for the human mannose receptor. J Virol 78, 4120-4133, PubMed: 15047828
186 Di Rienzo, A.M. et al. (1998) Virological and molecular parameters of HIV-1 infection of human embryonic astrocytes. Arch Virol 143, 1599-1615, PubMed: 9739337
187 Ranki, A. et al. (1995) Abundant expression of HIV Nef and Rev proteins in brain astrocytes in vivo is associated with dementia. Aids 9, 1001-1008, PubMed: 8527071
188 Neumann, M. et al. (1995) Restriction of human immunodeficiency virus type 1 production in a human astrocytoma cell line is associated with a cellular block in Rev function. J Virol 69, 2159-2167, PubMed: 7884864
189 Brengel-Pesce, K. et al. (1997) Transient infection of astrocytes with HIV-1 primary isolates derived from patients with and without AIDS dementia complex. J Neurovirol 3, 449-454, PubMed: 9475117
190 Gorry, P.R. et al. (1999) Diminished production of human immunodeficiency virus type 1 in astrocytes results from inefficient translation of gag, env, and nef mRNAs despite efficient expression of Tat and Rev. J Virol 73, 352-361, PubMed: 9847339
191 Rothstein, J.D. et al. (1996) Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. Neuron 16, 675-686, PubMed: 8785064
192 Rostasy, K. et al. (2003) SDF-1alpha is expressed in astrocytes and neurons in the AIDS dementia complex: an in vivo and in vitro study. J Neuropathol Exp Neurol 62, 617-626, PubMed: 12834106
193 Bezzi, P. et al. (2001) CXCR4-activated astrocyte glutamate release via TNFalpha: amplification by microglia triggers neurotoxicity. Nat Neurosci 4, 702-710, PubMed: 11426226
194 Fine, S.M. et al. (1996) Tumor necrosis factor alpha inhibits glutamate uptake by primary human astrocytes. Implications for pathogenesis of HIV-1 dementia. J Biol Chem 271, 15303-15306, PubMed: 8663435
195 Benos, D.J. et al. (1994) Cytokines and HIV envelope glycoprotein gp120 stimulate Na+/H+ exchange in astrocytes. J Biol Chem 269, 13811-13816, PubMed: 8188658
196 Bezzi, P. et al. (1998) Prostaglandins stimulate calcium-dependent glutamate release in astrocytes. Nature 391, 281-285, PubMed: 9440691
197 Piani, D. et al. (1993) Glutamate uptake by astrocytes is inhibited by reactive oxygen intermediates but not by other macrophage-derived molecules including cytokines, leukotrienes or platelet-activating factor. J Neuroimmunol 48, 99-104, PubMed: 7901235
198 Volterra, A. et al. (1994) Glutamate uptake inhibition by oxygen free radicals in rat cortical astrocytes. J Neurosci 14, 2924-2932, PubMed: 7910203
199 Wahl, L.M. et al. (1989) Human immunodeficiency virus glycoprotein (gp120) induction of monocyte arachidonic acid metabolites and interleukin 1. Proc Natl Acad Sci U S A 86, 621-625, PubMed: 2536171
200 Giulian, D. et al. (1988) Interleukin-1 injected into mammalian brain stimulates astrogliosis and neovascularization. J Neurosci 8, 2485-2490, PubMed: 2470873
201 Lee, S.C. et al. (1993) Induction of nitric oxide synthase activity in human astrocytes by interleukin-1 beta and interferon-gamma. J Neuroimmunol 46, 19-24, PubMed: 7689587
202 Rosenman, S.J. et al. (1995) Cytokine-induced expression of vascular cell adhesion molecule-1

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
©2005 Cambridge University Press

https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

(VCAM-1) by astrocytes and astrocytoma cell lines. J Immunol 154, 1888-1899, PubMed: 7530745
203 Woodman, S.E. et al. (1999) Human immunodeficiency virus type 1 TAT protein induces adhesion molecule expression in astrocytes. J Neurovirol 5, 678-684, PubMed: 10602408
204 Nagamura-Inoue, T., Tamura, T. and Ozato, K. (2001) Transcription factors that regulate growth and differentiation of myeloid cells. Int Rev Immunol 20, 83-105, PubMed: 11342299
205 Bradley, M.N., Zhou, L. and Smale, S.T. (2003) C/EBPbeta regulation in lipopolysaccharide-stimulated macrophages. Mol Cell Biol 23, 4841-4858, PubMed: 12832471
206 Akira, S. and Kishimoto, T. (1992) IL-6 and NF-IL6 in acute-phase response and viral infection. Immunol Rev 127, 25-50, PubMed: 1380488
207 Rosati, M. et al. (2001) CCAAT-enhancer-binding protein beta (C/EBP beta) activates CCR5 promoter: increased C/EBP beta and CCR5 in T lymphocytes from HIV-1-infected individuals. J Immunol 167, 1654-1662, PubMed: 11466389
208 Casola, A. et al. (2001) Multiple cis regulatory elements control RANTES promoter activity in alveolar epithelial cells infected with respiratory syncytial virus. J Virol 75, 6428-6439, PubMed: 11413310
209 Pan, Z., Hetherington, C.J. and Zhang, D.E. (1999) CCAAT/enhancer-binding protein activates the CD14 promoter and mediates transforming growth factor beta signaling in monocyte development. J Biol Chem 274, 23242-23248, PubMed: 10438498
210 Wang, H. et al. (2001) Platelet-activating factor and endotoxin activate CCAAT/enhancer binding protein in rat small intestine. Br J Pharmacol 133, 713-721, PubMed: 11429396
211 Ambrosino, C. et al. (1997) HIV-1 Tat induces the expression of the interleukin-6 (IL6) gene by binding to the IL6 leader RNA and by interacting with CAAT enhancer-binding protein beta (NF-IL6) transcription factors. J Biol Chem 272, 14883-14892, PubMed: 9169458
212 Liu, X. et al. (2002) Human immunodeficiency virus type 1 (HIV-1) tat induces nitric-oxide synthase in human astroglia. J Biol Chem 277, 39312-39319, PubMed: 12167619
213 Henderson, A.J. and Calame, K.L. (1997) CCAAT/enhancer binding protein (C/EBP) sites are required for HIV-1 replication in primary macrophages but not CD4(+) T cells. Proc Natl Acad Sci U S A 94, 8714-8719, PubMed: 9238043
214 Lee, E.S. et al. (2002) CCAAT/enhancer binding proteins are not required for HIV-1 entry but regulate proviral transcription by recruiting coactivators to the long-terminal repeat in monocytic cells. Virology 299, 20-31, PubMed: 12167337
215 Henderson, A.J., Zou, X. and Calame, K.L. (1995) C/EBP proteins activate transcription from the human immunodeficiency virus type 1 long terminal repeat in macrophages/monocytes. J Virol 69, 5337-5344, PubMed: 7636977
216 Komuro, I. et al. (2003) CSF-induced and HIV-1-mediated distinct regulation of Hck and C/EBPbeta represent a heterogeneous susceptibility of monocyte-derived macrophages to M-tropic HIV-1 infection. J Exp Med 198, 443-453, PubMed: 12900520
217 Ross, H.L. et al. (2001) HIV-1 LTR C/EBP binding site sequence configurations preferentially encountered in brain lead to enhanced C/EBP factor binding and increased LTR-specific activity. J Neurovirol 7, 235-249, PubMed: 11517398
218 Hogan, T.H. et al. (2003) Structural and functional evolution of human immunodeficiency virus type 1 long terminal repeat CCAAT/enhancer binding protein sites and their use as molecular markers for central nervous system disease progression. J Neurovirol 9, 55-68, PubMed: 12587069
219 Hogan, T.H. et al. (2003) HIV-1 Vpr binding to HIV-1 LTR C/EBP cis-acting elements and adjacent regions is sequence-specific. Biomed Pharmacother 57, 41-48, PubMed: 12642036
220 Burdo, T.H. et al. (2004) High-affinity interaction between HIV-1 Vpr and specific sequences that span the C/EBP and adjacent NF-kappaB sites within the HIV-1 LTR correlate with HIV-1-associated dementia. DNA Cell Biol 23, 261-269, PubMed: 15142383
221 Jones, K.A. et al. (1986) Activation of the AIDS retrovirus promoter by the cellular transcription factor, Sp1. Science 232, 755-759, PubMed: 3008338
222 Gaynor, R. (1992) Cellular transcription factors involved in the regulation of HIV-1 gene expression. Aids 6, 347-363, PubMed: 1616633
223 Peeters, A., Lambert, P.F. and Deacon, N.J. (1996) A fourth Sp1 site in the human immunodeficiency virus type 1 long terminal repeat is essential for negative-sense transcription. J Virol 70, 6665-6672, PubMed:

Accession information: DOI: 10.1017/S1462399405010239; Vol. 7; Issue 27; 2 December 2005
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https://doi.org/10.1017/S1462399405010239 Published online by Cambridge University Press

8794302
224 Li, J.M. et al. (1995) Transforming growth factor beta activates the promoter of cyclin-dependent kinase inhibitor p15INK4B through an Sp1 consensus site. J Biol Chem 270, 26750-26753, PubMed: 7592908
225 Nabel, G. and Baltimore, D. (1987) An inducible transcription factor activates expression of human immunodeficiency virus in T cells. Nature 326, 711-713, PubMed: 3031512
226 Brach, M.A. et al. (1991) Regulation of M-CSF expression by M-CSF: role of protein kinase C and transcription factor NF kappa B. Pathobiology 59, 284-288, PubMed: 1883525
227 Yang, Y., Tesmer, V.M. and Bina, M. (2002) Regulation of HIV-1 transcription in activated monocyte macrophages. Virology 299, 256-265, PubMed: 12202228
228 Shiramizu, B. et al. (2005) Circulating proviral HIV DNA and HIV-associated dementia. Aids 19, 45-52, PubMed: 15627032
229 Vehmas, A. et al. (2004) Amyloid precursor protein expression in circulating monocytes and brain macrophages from patients with HIV-associated cognitive impairment. J Neuroimmunol 157, 99-110, PubMed: 15579286
230 Corder, E.H. et al. (1998) HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. Nat Med 4, 1182-1184, PubMed: 9771753
231 Valcour, V. et al. (2004) Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. J Neuroimmunol 157, 197-202, PubMed: 15579298
232 Rothe, G. et al. (1996) Peripheral blood mononuclear phagocyte subpopulations as cellular markers in hypercholesterolemia. Arterioscler Thromb Vasc Biol 16, 1437-1447, PubMed: 8977447
233 Stohr, J. et al. (1998) Enhanced upregulation of the Fc gamma receptor IIIa (CD16a) during in vitro differentiation of ApoE4/4 monocytes. Arterioscler Thromb Vasc Biol 18, 1424-1432, PubMed: 9743231
234 Kalter, D.C. et al. (1991) Enhanced HIV replication in macrophage colony-stimulating factor-treated monocytes. J Immunol 146, 298-306, PubMed: 1701795
235 Rempel, H.C. and Pulliam, L. (2005) HIV-1 Tat inhibits neprilysin and elevates amyloid beta. Aids 19, 127-135, PubMed: 15668537
236 Zink, M.C. et al. (2005) Neuroprotective and anti-human immunodeficiency virus activity of minocycline. Jama 293, 2003-2011, PubMed: 15855434
237 Muller, W.E. et al. (1992) gp120 of HIV-1 induces apoptosis in rat cortical cell cultures: prevention by memantine. Eur J Pharmacol 226, 209-214, PubMed: 1426020
238 Toggas, S.M., Masliah, E. and Mucke, L. (1996) Prevention of HIV-1 gp120-induced neuronal damage in the central nervous system of transgenic mice by the NMDA receptor antagonist memantine. Brain Res 706, 303-307, PubMed: 8822372
239 Anderson, E.R., Gendelman, H.E. and Xiong, H. (2004) Memantine protects hippocampal neuronal function in murine human immunodeficiency virus type 1 encephalitis. J Neurosci 24, 7194-7198, PubMed: 15306653
240 Thomas, D.M. and Kuhn, D.M. (2005) MK-801 and dextromethorphan block microglial activation and protect against methamphetamine-induced neurotoxicity. Brain Res 1050, 190-198, PubMed: 15987631
241 Dou, H. et al. (2004) Neuroprotective strategies for HIV-1 associated dementia. Neurotox Res 6, 503-521, PubMed: 15639783
242 Kaul, M. and Lipton, S.A. (2004) Signaling pathways to neuronal damage and apoptosis in human immunodeficiency virus type 1-associated dementia: Chemokine receptors, excitotoxicity, and beyond. J Neurovirol 10 Suppl 1, 97-101, PubMed: 14982746

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Further reading, resources and contacts

The December 2004 issue (Vol. 157, Issues 1–2) of *Journal of Neuroimmunology* includes articles on molecular markers and mechanisms of HIV-induced nervous system disease.

The 2005 Supplement 1 issue (Vol. 11) of *Journal of NeuroVirology* presents current articles discussing AIDS and neuroAIDS in Africa.

Features associated with this article

Figures

Figure 1. Possible mechanisms in neuronal injury and apoptosis in HIV-D.
Figure 2. Select cytokine-inducible regions in the HIV-1 LTR.

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