

PATHOGENIC MECHANISMS OF HIV-1 ENCEPHALITIS

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ABSTRACT

Human immunodeficiency virus type 1 (HIV-1) is a member of Lentivirus genus of retroviruses that can determine a relatively slow encephalitis. The pathogenesis of HIV-1 encephalitis (HIVE) can be discussed in terms of neuroinvasion, neurotropism and neurovirulence. Several mechanisms are implicated in the pathogenesis, some of them being still under investigation.

Key words: encephalitis, HIV-1, pathogeny.

BACKGROUND

HIV-1, a member of Lentivirus genus of retroviruses, can determine a relatively slow encephalitis, the neurological changes consisting in cognitive, behavior and motor dysfunctions.

HIV-1 encephalitis is linked to HIV-1 associated dementia, a common source of morbidity in HIV patients, HIV-1 infection being the most common cause of dementia in young adults (1). Although HIV-1 invades the brain early after exposure (2), the neurological impairments occur years after viral exposure and are associated with depletion of CD4+ T lymphocytes and high viral loads.

The introduction of highly active antiretroviral therapy (HAART) determined the increase of life expectancy of the patients and the decrease of the number of patients developing dementia, but it have been reported an increased rate of the minor cognitive motor disorders.

The pathogenesis HIVE can be discussed in terms of neuroinvasion, neurotropism and neurovirulence. Several mechanisms were implicated in the pathogenesis, some of them being still under investigation.

MORPHOPATHOLOGY

HIVE is characterized by macrophagic infiltration of central nervous system (CNS), a reactive astrocytosis and microgliosis. The most common pathologic finding is the presence of multinucleated giant cells resulting from the fusion of mononuclear phagocytes (MPs) with uninfected cells (3), typically occurring in the deep brain structures and white

subcortical matter. Also, in the brain there is a neuronal loss (especially in hippocampus, basal ganglia and caudate nucleus) and a variable degree of myelin damage, ranging from pallor to widespread lesions.

HIV-1 NEUROINVASION

HIV-1 neuroinvasion occurs early after primary infection, HIV antigens and genomes being detected in the CNS at all stages of infection (4, 5).

The sources of CNS infection are infected CD4+ T cells and monocytes (6). HIV-1 infects cells containing major HIV-1 receptors (CD4 and CD8) and chemokines receptors (HIV-1 coreceptors such as CXCR4 and CCR5). CXCR4 is the major coreceptors for lymphocytes and CCR5 for monocytes, macrophages and microglia (7).

The blood-brain barrier (BBB) is very restrictive due to the tight junctions between brain microvascular endothelial cells (BMVEC) and the astrocytes foot processes. BMVEC presents the intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) that permits the emigration of cells after attachment and release. During HIV-1 infection, ICAM-1 and VCAM-1 are often up-regulated on BMVEC and influence the leucocytes migration across the BBB (8).

Additionally, in HIVE, at the sites of inflammation chemokines are secreted that influence the leukocyte migration and proinflammatory cytokines (such as tumor necrosis factor α – TNF α , interleukin 1b). The cytokines enhance cell adhesion (9) and increase the endothelial permeability by

increasing the secretion of endothelial vasoactive factors (such as nitric oxide) (10).

The generally accepted hypothesis of HIV-1 neuroinvasion is the “Trojan horse” model (11). According to this model, HIV-1 enters into CNS using infected T cells and monocytes. This model was confirmed by *in situ* hybridization and immunohistochemical studies that demonstrated the accumulation of viruses in perivascular regions (12, 13).

An alternative pathway for entry into CNS can be through choroids plexus. There are studies that analyzing the viral sequences from choroids plexus, found viruses of differing tropism including potentially macrophage or T-cell tropic strains (14).

HIV-1 NEUROTROPISM

Regarding the HIV-1 neurotropism, theoretically, all cell types of CNS (perivascular macrophage and microglia, astrocytes, oligodendrocytes, neurons) can be infected since they present receptors and/or coreceptors for HIV-1, but the most commonly infected are the macrophages and microglia (6).

Two types of infection can occur into the CNS:

1. “productive infection” – the infected cells support productive viral replication, the transmission of the infection and the rapid evolution of the viral genome in the host;

2. “restricted infection” – the low or non-producers of viruses cells are permissive to HIV-1 strains, but are refractory to efficient virus expression; they survive as reservoir and changes in cell environment such as elevation of cytokines level (TNF α , IL1 β) might reactivate virus production (15).

Macrophages and microglia

The main sources of “productive infection” of CNS are the monocytes-derived macrophages and the microglia (16).

As the monocytes arrive into CNS, they differentiate into macrophages (multinucleated giant cells expressing CD4). Macrophages contain high levels of intracellular virus and act as antigen-presenting cells. They produce a wide range of immune factors as IFN α , IFN β , IL1 α , IL1 β , IL6, TNF α , and TNF β , which can affect the neural functions. Activation of macrophages can be due to proinflammatory cytokines or chemokines.

Microglial cells express CD4 major receptors and CCR5 coreceptors used by HIV-1 (17, 18), but contrasting to macrophages, they are weak antigen presenters. They also express chemokines receptors such as CCR3, CCR2b, CCR8, CXCR6, CX3CR1, but they are less efficiently used by HIV-1 (18, 19).

The infection of microglia is sustained by immunostaining studies that showed that sometimes the infection is widespread, but in other cases it is restricted to the perivascular region (20). It is still not clear if the HIV-1 immunopositive microglia consists of an influx of infected cells from the blood or results from long-term infection of CNS.

Astrocytes

Astrocytes do not have CD4 receptor, but they present CXCR4 and possibly other HIV-1 coreceptors including CCR5 (21). Some researchers report immunopositive astrocytes for HIV-1 structural proteins (22), but the mechanism of viral attachment is not clear. Other studies, using *in situ* hybridization or PCR demonstrated the presence of HIV-1 specific nucleic acids in astrocytes (12).

In HIV-1 infection, the astrocyte reuptake of glutamate is impaired by gp120 (23), and the activated macrophages induce additionally the release of glutamate (24). The viral proteins and cytokines determine the induction of inducible nitric oxide synthase in astrocytes, providing a link between inflammation and neurotoxicity (25).

Oligodendrocytes

Oligodendrocytes do not have CD4 receptors. Their infection by HIV-1 is controversial: *in vivo* studies have detected by *in situ* PCR viral nucleic acids (26), *in vitro* studies suggest that the cell types are permissive to certain strains of HIV (27), but other studies reported the absence of HIV-1 markers (28). The mechanism of their assumed infection is still not clear.

Neurons

In vivo infection of neurons is still controversial. Although many authors reported the absence of *in vivo* infection, there are studies which have detected HIV genome in neurons using *in situ* PCR (26). Some researchers suggested that the difficulties to detect infected neurons might be due to the loss of the infected populations (6).

Neuronal injury can be the result of a direct mechanism (by interaction with viral proteins produced by infected cells) or of an indirect mechanism that implies the inflammation (29).

HIV-1 NEUROVIRULENCE

Neurovirulence is the ability of the virus to cause disease.

In vitro studies indicate that HIV-1 strains differ in cytotoxicity, there being distinct HIV-1 envelope

sequences that influence the ability of viruses to infect specific cell types. Comparative studies between AIDS patients with and without dementia show different specific mutations within V1 (30) and V3 (31) domains of brain-derived HIV-1 envelope sequences. These domains also determine the ability of infectious recombinant clones to infect and spread in macrophages and glial cultures (30).

Viral proteins

Transcriptional transactivator – Tat can injury the neurons by direct or indirect mechanisms (32), acting at different levels.

Tat can determine an increase of intracellular calcium, followed by an increase of reactive oxygen species and activation of apoptosis (32, 33).

At the BBB level, Tat increases endothelial permeability altering the expression of tight junction proteins claudin 1 and claudin 5, enabling the infiltration of inflammatory cells into brain (34).

The expression of Tat in CD4 T cells determines the up-regulation of caspase-8, fact that contributes to an increase of apoptosis and a high sensitivity to apoptotic signals (35). Also, Tat promotes the monocytic and macrophagic production of TNF α and IL1 and stimulates the astrocytic production of cytokines and chemokines (such as TNF α , IL8, macrophage chemotactic protein 1 – MCP-1, RANTES), having a neurotoxic effect.

Viral protein R – Vpr is implicated in the direct mechanism of neuronal damage (36). It increases the activation of caspase-8 and determines apoptosis of neuronal precursor cells and mature neurons (37). At the mitochondrial level, Vpr alters the mitochondrial permeability releasing the cytochrome C, fact that can lead to apoptosis (38); it also targets an antiapoptotic mitochondrial protein (HAX-1), dislocating it from its normal residence, causing mitochondrial instability and apoptosis (39).

Glycoprotein 120 – gp120 has been shown to induce injury and apoptosis in animal and human neurons *in vitro* and *in vivo*. Apoptosis occurs via direct interaction of gp120 with neurons or indirectly, by stimulating the release of neurotoxic factors.

Neuronal degeneration can result directly through the interaction between gp120 and NMDA receptors (40). Also, it has been demonstrate that gp120 and Tat impair the calcium-regulating systems of the membrane and endoplasmatic reticulum, leading to neuronal death (41). The dopaminergic neurons are more susceptible to gp120 neurotoxicity (42).

The indirect mechanism results from the interactions of gp120 with macrophages, microglia

and astrocytes (43). Gp120 induces the release of neurotoxic substances such as EAAs, arachidonic acid and related molecules (e.g. PAF) which engenders neuronal glutamate release. The interaction of gp120 with astrocytes determines the stimulation of the inducible form of nitric oxide synthetase and increases the release of arachidonic acid from astrocytes, leading to the inhibition of glutamate uptake by astrocytes and neurons (44). The high levels of extracellular glutamate might have neurotoxic effects by activating the excitatory amino-acid receptors on neurons.

Gp120 also triggers a signaling pathway that involves p38 mitogen activated protein-kinase, a pivotal factor in immune stimulation of macrophages (45).

HIV-1 ASSOCIATED CHEMOKINES

The neuronal apoptosis can also be influenced by chemokines, they being considered to be the gate of entrance of HIV into CNS (46).

Several chemokines show enhanced expression in the brain of HIV infected patients. CCR2, CCR3 and CXCR4 HIV-1 coreceptors were found in neurons (47) and glial cells, the areas with highest expression being the subcortical regions and the limbic system (29). In the microglial nodules were found elevated levels of expression of CCR1, CCR3, CCR5 and CXCR4 (48). The role of CCR5, expressed by neurons, microglia and astrocytes is controversial. Activation of CCR5 from the neuronal surface by RANTES or macrophage inflammatory protein MIP-1 has been demonstrated to attenuate gp120 and NMDA toxicity (45).

HIV-1 PROINFLAMMATORY CYTOKINES

It has been demonstrated that in the brain and CSF of patients with HIV multiple cytokine are elevated.

The monocytes, lymphocytes, activated macrophages, microglia and astrocytes release cytokines, reactive oxygen species and other neurotoxins which determine impairments in cellular functioning, modify neurotransmitters action and might lead to leukoencephalopathy and neuronal apoptosis (49).

Macrophages secrete IFN α , IFN β , IL1 α , IL1 β , TNF α and TNF β . Also, activated macrophages produce EAAs, reactive species of oxygen and nitric oxide (NO). An EAA is the *quinolinate*, and it acts through the neuronal NMDA subtype of glutamate receptors inducing excitotoxicity (16). Other EAAs that stimulate the NMDA receptors are *glutamate* and *L-cysteine* (50).

In response to $TNF\alpha$, macrophages secrete PAF, causing glutamate release and increased cellular calcium influx (51).

$TNF\alpha$ is released by infected macrophages and microglia and particularly affects oligodendrocytes (52). It also increases the BBB permeability (10). The increased permeability might permit the influx into brain of neurotoxins such as arachidonic acid metabolites (53), quinolinic acid (54) and chemokines (55).

$IL\ 1\ \beta$ and $TNF\ \alpha$ induce a transitive increasing of BBB permeability by determining an increased secretion of endothelial vasoactive factors such as nitric oxide (NO) (10). They also increase the production of other inflammatory mediators such as arachidonic acid, derived platelet activating factor,

enhancing cell migration and neurotoxic reactions (56).

NO is synthesized by endothelial cells, macrophages and neurons. It is associated with the NMDA type glutamate neurotoxicity.

Some neurotrophic molecules such as TGF α and nerve growth factor have been found to be over-expressed in HIVE (57). Their increased production might reflect a host defense response to the neurotoxic actions of HIV-1.

All this data suggest that HIVE is a complex problem, being the result of many mechanisms implicating a large numbers of factors. Some of them still need to be investigated, the pathogenic mechanisms of CNS infection by HIV-1 being far to be elucidated.

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