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Brain Aging in HIV-1 Infection

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Abstract

It has been shown that patients carrying HIV-1 accumulate damage to cells and tissues that are not directly infected by the virus itself (e.g., neurons). Importantly, these include changes known as HIV-Associated Neurodegenerative Disorder (HAND) leading to the loss of neuronal functions. HAND is an outstanding problem in the clinical management of HIV-1 patients because suppression of infectious virus by c-ART does not completely block neurodegenerative changes. Neuropsychological studies disclose cognitive alteration (such as loss of Spatial and Declarative Memory) in a substantial proportion of HIV-1 infected patients, and analysis of post-mortem brain tissues isolated from HIV-1 patients treated with c-ART show signs of neurodegeneration. In the absence of HIV-1 infection of neurons, several mechanisms have been proposed for HAND, including indirect inflammatory effects in the CNS and direct effects of viral proteins (e.g., gp120) shed from activated HIV-1-infected cells. The fact that these viral proteins enter the neurons through several pathways suggests the presence of many competing mechanisms that can contribute to HAND, each of which has its advocates. Their relative contributions to clinical disease in vivo remain to be sorted out, and this is an outstanding problem in HIV research. This chapter will shed some light on the mechanisms used by HIV-1 leading to memory impairments and premature brain aging.

Keywords: HIV, brain, aging, mitochondria

1. HIV-1 and structural changes

1.1. Thinning of the cortex: white/gray matter (methods and results)

Physiological brain aging is associated with a decrease in gray matter (GM) volume between adulthood and old age, while the volume of white matter (WM) increase from age 19 to 40 and will regress after that [1]. *The reduction of gray matter is probably the result of neuronal shrinkage*

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and the reduction of synaptic spines [2]. Ventricular enlargement associated with normal aging and the Evans' index is used to distinguish normal and pathological enlargement [3].

Different techniques are used to evaluate different categories of brain changes: neurophysiology, neurochemistry, brain structure, and brain activation networks. Structural magnetic resonance imaging (MRI), diffusion MRI, and X-ray computed tomography (CT) are the tools for structural neuroimaging. Neurometabolites or neurochemicals can be tracked with positron emission tomography (PET) using radiotracers and by magnetic resonance spectroscopy (MRS). Brain activation networks can be studied by functional magnetic resonance imaging (fMRI) methods based on blood oxygenation level-dependent (BOLD) contrast, and arterial spin labeling (ASL) perfusion contrast shows changes in cerebral blood flow (CBF) and blood oxygenation.

Using imaging techniques, scientists and clinicians determined that the global cerebral volume is smaller in HIV-1 patients than in the seronegative population [4]. The HIV+ subjects also present a higher neuronal loss [5] and the patients with detectable viral loads had the highest rates of gray (GM) and white (WM) matter loss [6].

MRI technique also revealed that the gray matter of HIV+ subjects may present cortical atrophy [7, 8] and volumetric loss in the caudate, amygdala, and hippocampus [4, 7, 9–12]. Moreover, the medial and superior frontal gyri can show an atrophy [13], as well as the posterior and inferior temporal lobe, parietal lobe, and cerebellum [14].

If changes of white matter integrity are common with age, the abnormalities are more pronounced in aged HIV+ subjects [15]. The white matter of HIV+ subjects displayed some changes, like a tissue loss in the corpus callosum [9], as well as corpus callosum thinning and ventricular expansion [16]. HIV+ subjects showed increased mean diffusivity in frontal and parietal white matter, putamen, and genu [17]. Lower fractional anisotropy is also found at an older age in HIV+ subjects in white matter of frontal, temporal, and parietal lobes but a higher mean diffusion only in the occipital white matter [18]. Small white matter hyperintensities (WMH) are associated with age in seronegative adults [19, 20] and are attributed to inflammatory, vascular, or blood–brain barrier changes [21, 22]. However, these WMHs can be connected to dementia, multiple sclerosis, and cerebrovascular diseases [23, 24]. The increase of WMH volume is linked to lesser brain integrity in the sagittal stratum and the corpus callosum. HIV+ adults over age 60 showed a higher ratio from abnormal to normal WMH, with a subset of individuals in this age group with a significantly high WMH. This high ratio is associated with cardiovascular and is inversely correlated with global psychomotor and cognitive performance. The examination of the microstructure of the white matter by diffusion tensor imaging (DTI) brings a promising disease-activity marker [25]. A disease more advanced associated with a higher rate of decline of the CD4 count is linked to a greater atrophy of the gray and white matter in the brain [26].

Away from human, this degeneration in gray and white matter was also observed in HIV-1 Tat transgenic mice model. The expression of Tat protein diminishes cortical gray matter density in young Tat transgenic mice [27] and alters the structure of myelin examined by either DTI imaging [28] or electron microscopy [29], with declines of fractional anisotropy and behavioral changes.

Finally, more developed tools and methods (e.g., brain PAD) were also used to measure the influence of HIV-1 on aging. This integrative tool measures brain-predicted age difference (brain-PAD) scores. It associates structural neuroimaging data with neuropsychological test scores, trying to predict brain age and to assess the correlation of brain age to chronological age [30].

1.2. Loss of neural circuits and brain plasticity: implication of long-term potentiation in learning and memory

Long-term potentiation (LTP) is a persistent increase in the synaptic activity leading to the signal transmission between two neurons. The canonical mode of LTP induction at CA1 hippocampal synapses relies on the glutamate receptor NMDAR and the following biochemical cascade triggered and maintained by the synaptic protein calcium/calmodulin-dependent protein kinase II (CaMKII). The impairment of this cascade would lead to an acute deficit in learning and memory storage. LTP is involved in learning and memory functions in structures like the hippocampus or the amygdala. It is generated by short repetitive high-frequency stimulation (HFS) and may persist for hours or days.

An early study in 1999 demonstrated that some factors secreted by HIV-1-infected monocytes-derived macrophages (MDMs) inhibit the induction of LTP in the CA1 region of the rat hippocampus [31]. Later, a study shows that mice with severe combined immunodeficiency (SCIDs) injected by HIV-1-infected human monocyte-derived macrophages (MDMs) into the basal ganglia present a gradual decrease in synaptic function, followed by decreased cognition and later by an impairment of multiple phases of synaptic potentiation [32]. Impairment of synaptic functions, as well as the induction and maintenance of LTP, is described in mice with HIVE [33]. HIV-infected brain mononuclear phagocytes (MP) (macrophages and microglia) are the reservoirs for persistent viral infection. They secrete soluble factors like chemokines, free radicals, proinflammatory cytokines, nitric oxide, and eicosanoids. HIV-infected MDM culture supernatants containing same soluble factors have the capability to inhibit synaptic transmission and block LTP from the CA1 part of the hippocampus of rats. A deeper investigation of the mechanism involved shows that IL-8 severely reduces Ca^{2+} currents in the septal neurons, triggering the closure of L- and N-type Ca^{2+} channels [34]. Without an increase of the intracellular Ca^{2+} flux, the LTP in the CA1 region of the hippocampus is impaired [35].

The study of isolated HIV-1 proteins on CA1 long-term potentiation (LTP) gave us more information about the mechanisms involved in the impairment of learning and memory by HIV-1. Mice-expressing HIV-1 gp120 are showing a significant decrease in CA1 hippocampal LTP. Gp120-induced impairment is prevented by a pre-treatment with the NMDA receptor antagonist, suggesting that excessive activation of the NMDA receptor, that can lead to excitotoxic cell death, is responsible for the degenerative process triggered by gp120 [36]. HIV-1 gp120 protein inhibits LTP via the chemokine receptor CXCR4 and binds to it through the V3 loop epitope KRIHI [37]. Gp120-associated reduction of LTP is alleviated by a systemic administration of 4-AP, a Kv, channel antagonist. This result supports the evidence that the neuronal voltage-gated potassium (K^+) channels (Kv) are targeted by gp120 during the inhibition of LTP and that Kv channels are linked learning and memory deficiencies in HAND [38]. With normal, non-pathological aging, dendritic trees experience gradual regression in dendritic arbors

of pyramidal neurons situated in the superior temporal, precentral, and prefrontal cortices in humans [8]. HIV-1 Tat expression in pyramidal CA1 neurons decrease the number of apical dendritic spines, without the evidence of pyramidal death but with the disruption of the distribution of the synaptic proteins gephyrin and synaptogtagmin2 [39]. The Tat expression induces synapto-dendritic modifications in the hippocampus that will disrupt the LTP in CA1 pyramidal neurons and subsequently bring deficits in learning and memory.

HIV-1 Tat protein injection into the hippocampus showed that Tat plays on extra-synaptic NMDA receptors but not on synaptic. Additionally, it suppresses long-term potentiation (LTP) followed by a diminution of spatial learning. Tat protein induces the phosphorylation of NMDA receptor subunits NR2A and NR2B in a tyrosine kinase-dependent manner, which triggers Ca^{2+} flux. Ca^{2+} entry through synaptic NMDA receptors activates cAMP response element binding protein (CREB) activity, and confers antiapoptotic ability, while Ca^{2+} entry through extrasynaptic NMDA receptors shuts off CREB pathway [40]. Some recent work shows that CREB protein holds an essential role in memory formation. CREB protein brings changes in global neuronal excitability. CREB overexpression results in more action potential for each pulse and a smaller after-hyperpolarization (AHP) after a chain of action potentials. AHP is usually engendered by K^+ channels, and CREB might be involved in variations in K^+ conductance. By enhancing neuronal excitability, CREB might increase the inclusion of neurons into the memory trace [41].

2. Neuropsychological changes

2.1. Depression: serotonin loss

With normal aging, the brain suffers from serotonin (5-HT) neuron and neurotransmitter loss. This deficit in serotonergic neurotransmission might promote the occurrence of depression in the elderly population [42]. The incidence of major depression is estimated from 1 to 10% in a population older than 60 years of age, while depressive symptoms may affect up to 20% [43, 44]. Even if it is not considered as a normal aging event, the loss of serotonin and subsequent depression is a common even among the elderly.

Depression is significant comorbidity with a prevalence superior to 30% in some studies in HIV-infected patients [45, 46]. Among a cohort of 13,874 HIV-infected patients, 44% percent of the study population had depression, and 15% of the whole cohort was prescribed SSRIs [47].

The essential amino acid l-tryptophan (Trp) is the precursor of some essential metabolites produced during the course of its degradation, along with different pathways, like the kynurenine (KYN) pathway and the serotonin, 5-hydroxytryptamine or 5-HT pathway. During the kynurenine pathway, the tryptophan is converted by the enzymes Tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase 1 (IDO1), IDO2. The resulting product is further degraded to kynurenine (KYN), which is a precursor of bioactive compounds, including quinolinic acid (QUIN), that subsequently activate or inhibit NMDA neurotransmission. Pro-inflammatory cytokines, including interferon-γ (IFN-γ), interleukin-1 β (IL-1β), and IL-6, can further induce IDO-1 and TDO and thus activate this pathway, reducing the availability of TRP for the serotonin synthesis pathway [48–51].

HIV-1 clade B Tat is responsible for the up-regulation of IDO and the down-regulation of 5-HT gene and protein expressions. Also, HIV-1 clade B Tat reduces 5-HT with a concomitant increase in KYN levels as compared to HIV-1 clade C Tat [52].

HIV+ subjects present a reduced breakdown of Phe to tyrosine (Tyr) [53, 54] and a faster conversion of trp to kynurenine (Kyn) [55], which is correlated with higher levels of immune activation markers like interferon-γ (IFN-γ) or neopterin in HIV-1 individuals [56]. Accelerated trp breakdown was correlated with neuropsychiatric symptoms in HIV patients [55, 57].

It is interesting to note that serotonin treatment decreases the HIV-I replication in human macrophages. Indeed 5-HT decreases the β-chemokine receptor, CCR5, and increases the CCL5 chemokine, MIP-1α, implying an effect of 5-HT on 5-HT1A receptors on macrophages [58]. Further, some studies show that in HIV+ individuals the blocking of the re-uptake of serotonin (SSRIs) is associated with the up-regulation of NK cells [59, 60]. Serotonergic pathways are important in the function of natural killer (NK) cells and CD8 + T cells [61].

2.2. HIV-1 and risks of Alzheimer's disease (AD) pathogenesis

Apolipoprotein (apo) E isoforms (apoE2, apoE3, and apoE4) play a role in cardiovascular disease and lipoprotein metabolism but are mainly studied for their contribution in neurodegeneration in Alzheimer's disease [62–64]. HIV-associated dementia (HAD) is a neurological condition with clinicopathological features similar to Alzheimer's disease [65].

Early research presented in Nature Medicine in 1998 measures the risk of dementia in patients who presented E4 isoform for apolipoprotein E (APOE). Compared to the normal subjects, they presented twice more dementia and peripheral neuropathy, concluding that a long-term infection brings an increased risk of dementia for E4(+) subjects [66], with an even bigger risk with low CD4+ cell count and length of infection. It is today widely accepted that the *APOE* ε4/ε4 genotype is associated with a faster disease course and progression to death compared with the *APOE* ε3/ε3 genotype. However, an association between the ε4/ε4 genotype and HIV-associated dementia (HAD) was not identified [67].

APOEε4 allele(s) may lead to premature aging with neurodegeneration in younger HIV patients preceding the development of HAND, potentially because of greater neuroinflammation or more abundant amyloid deposition in younger HIV subjects with APOEε4 allele(s) [4, 68]. Recent neuroimaging studies present conflicting results. One study on 237 patients shows that the ApoEε4 allele does not affect brain integrity, gray, or white matter, in their cohort of HIV+ individuals [69]. Another study on 76 patients shows brain atrophy, especially in the posterior corpus callosum, thalamus, and brainstem [70]. These individuals were older than 60, which could explain the discrepancy between the studies; the deleterious effects could be age dependent [71].

The APOEε4 genotype is a risk factor for elevated cholesterol in ART-adherent HIV(+) men aged >50 years [72] with a risk for a higher cognitive decline associated and cardiovascular problems.

All these studies taken together, it is now clear that individuals with HIV and the ApoE gene exhibited greater cognitive deficits when tested for attention, executive function, and working memory than HIV-infected individuals with ApoE4 genotype carriers.

3. Gait/balance

Aging is associated with a cascade of events affecting the function of the Substantia Nigra (SN) neurons, from the dopamine metabolism to the mitochondrial dysfunction and the alteration in protein degradation. The addition of cellular defects linked to aging increases the risks of developing Parkinson's disease [73, 74].

With aging, the density of dopamine transporters and dopaminergic neurons decreases, and there is a correlation between the decline of the dopamine system function and the executive function [75]. Several studies show evidence of a link between aging, memory, learning, and dopaminergic change [76–79]. HIV-1 penetrates the brain immediately after the initial infection and is disseminated in various concentrations in different parts of the brain, with a particular affinity for the subcortical regions like the basal ganglia, including the putamen, caudate nucleus, globus pallidus, and Substantia Nigra [80]. HIV-1 RNA is also identified in different regions of the postmortem brain, especially in different nuclei of the basal ganglia [81–83]. Since basal ganglia is the main target of HIV infection in the brain, it is not surprising that the dopaminergic function located in the Substantia Nigra will be altered. Neuropathological assessments of HIV+ patients show that the degeneration of Substantia Nigra is common. Moreover, it could explain the sensitivity of some patients to drug-induced Parkinsonism [84].

HIV-1 and Parkinson's disease both affect nigrostriatal structures with subsequent dopaminergic dysfunction. HIV-1 patients display signs of hypomimia, bradykinesia, poor hand agility, and action or postural tremor exacerbated by age [85]. The aging HIV+ population treated with HAART shows more frequent presentation of HIV-1 Parkinsonism. A significant decrease of dopamine in the Substantia Nigra was subsequently found in the postmortem examination of the HIV+ brains [86]. Alpha-synuclein is one of the major factors in Parkinson's disease pathology, and its expression was found to have increased in the Substantia Nigra of HIV+ postmortem brain [87]. Alpha-synuclein plays a role in the apoptosis of dopamine cells and reinforces the idea that the aging brain of HIV+ individuals may develop PD. Different studies report that the dopamine concentration in the HIV-infected brain can decrease by 50% [80, 86, 88]. The decrease in DA levels in SN was significantly correlated with the decrease in performance in learning, memory, speed of processing information, and verbal fluency.

The presynaptic dopamine transporter (DAT)-mediated dopamine reuptake is crucial for regular dopamine homeostasis and subsequent brain functions like memory, learning, and attention. However, it has been reported that HIV patients with dementia had substantially lower DAT availability in ventral striatum and putamen [89]. The DAT expression and function is also altered by HIV proteins in animals. HIV-1 Tat induces inhibition of the transporter by an allosteric binding to DAT [90]. DAT function and expression is modified in the HIV-1-tg rats [91]. HIV-1 gp120 was similarly described to cause a loss of dopamine-secreting neurons in rats [92–94]. HIV-1 Nef is another viral protein disturbing the dopamine functions, reducing striatal dopamine levels in HIV-1 mice. The animal will consequently develop mania-like behaviors and present a reduced content of dopamine and DAT [95].

HIV+ subjects present a diminished motor performance at multitasking and a decreased velocity compared to the control group. This may affect the daily life and require more attention to

every motor task [96]. A psychomotor slowing of HIV patients was already described in early neuropsychological studies [97], which was presumed to be from the frontostriatal origin. The first hypothesis for the gait and balance problems was a neuropathy of the peripheral nervous system [98, 99]. However, the cerebellum, and the pons more exactly, is also implicated in HIV infection [100–105].

There is evidence of cerebellar damage [105–107] and an important degeneration of the cerebellar granular cell layer and axonal swelling. CT and MRI show pontocerebellar damage in HIV infection [108] and 3–6% of an HIV-infected group [109]. Men and women show tissue volume deficits in combined pons, vermis tissue, and cerebellar hemispheres. This will result in a deficit in motor performance like static postural stability, and tandem walking, particularly when the patients have their eyes closed during the test. The psychomotor speed and the finger dexterity were also impaired.

The pediatric HIV-1 infection will present different complications, involving deep abnormalities in the striatal dopamine system including the basal ganglia. The HIV-infected children present a slower-than-normal information processing and poor attentional abilities [110–112].

4. Epigenetic changes

4.1. Methylation levels

Epigenetic alterations are one of the hallmarks of aging. As epigenetic changes accumulate upon aging, DNA methylation can be a precise predictor of chronological age [113, 114], since certain CpG sites are highly associated with age [115].

A first large-scale epigenome-wide association study in 2016 analyzed DNA methylation during HIV infection [116] and found a differential DNA methylation associated with the infection. HIV-1, as other viruses, can alter the expression of DNA methyltransferases (DNMTs), like DNMT1 [117, 118] and DNMT3b [119], affecting maintenance and de novo DNA methylation maintenance. The alteration of methylation could be an epigenetic outcome of the integration of HIV-1 DNA into the host genome and could decrease genome stability. These studies were made in blood, and because of the presence of the blood-brain barrier, it was necessary to analyze methylation directly in the brain tissue.

A 2015 study uses blood and brain tissue to find a relationship between HIV status and epigenetic age acceleration [120]. It eliminates different hypothesis explaining age acceleration effects in the brain tissue. It concluded that the telomere length is not involved and finds difficult to explain the age acceleration in the brain by the increase in the amount of senescent or exhausted T-cells like it is working in the blood, because of the blood-brain barrier. The retained hypothesis is an effect of the age acceleration, and independently the T-cells exhaust, confounding the relationship between these two events. In 2016, a comparative DNA methylation profiling on monocytes derived from HIV-infected individuals, with or without impairment, identifies a specific immunoepigenetic signature of cognitive impairment [121]. A total of 1032 loci differentially methylated are associated with cognitive impairment, with

loci connected to gene networks in the central nervous system and preferentially located in intergenic regions of the gene and over gene bodies. A more recent analysis was made on DNA from the occipital cortex of 58 HIV+ subjects that were followed for neurocognitive evaluation within 1 year of death [122]. It is the first study to associate HAND status with the epigenetic age of frontal cortex tissue, with an average relative acceleration of 3.5 years. This accelerated epigenetic aging was not the consequence of CD4+ cell count or viral load, the activity of HAART on the CNS, or comorbidities. Interestingly, the entire HAND group presented accelerated aging in the brain tissue, but that was not correlated with HAND gravity or neurocognitive performance. This accelerated aging seems linked to the duration of the infection and suggests that a low level but chronic HIV replication in brain reservoirs maintains pathological processes.

4.2. microRNA

The genome-wide expression analysis of miRNA in aging brains showed a unique expression profile which emphasizes how crucial their role is in the neurodegeneration and the aging process [123].

MiR-34a has been linked to the regulation of several proteins including sirtuin 1 (SIRT1) [124]. SIRT1 is an enzyme implicated in the deacetylation of proteins involved in cell stress, longevity, and glucose metabolism [125]. Mir-34a up-regulation, the reciprocal decline of its target SIRT1, is the biomarker for aging in the brain and a good predictor of deterioration of the brain function. The miR-34a expression is significantly increased in HIV-infected vascular endothelial cells (ECs) [126] as well as in primary neuronal cultures and neuronal cell lines [127]. MiR-146a was also up-regulated in these cells. HIV-1 vpr has the same ability to strongly overexpress miR-34a and miR-146a in neuronal cells and to down-regulate miR-106a [128]. The up-regulation of miR-34a and miR146a [129] and the down-regulation of miR-106a [130] are described to be associated with aging. The increase of miR-34a can cause abnormal mitochondrial dynamics and dysfunctional autophagy [131].

4.3. HIV-1 disrupts the calcium signaling in the brain

Changes in calcium signaling are major factors leading to aging, as many vital functions of the brain depend on precise calcium homeostasis [132]. Khachaturian presented in 1994 his hypothesis of aging [133] to try to elucidate the neurophysiological mechanisms of Ca^{2+} signaling that they are associated with aging and neurodegeneration.

HIV-1 disturbs the functional expression and activity of voltage-gated calcium channel (VGCCs) (changes in evoked Ca^{2+} spikes and L-channel expression) in the mPFC in an age-dependent way and implies that ion-channel dysfunction associated with HIV-induced medial PreFrontal Cortex (mPFC) hyper-excitability progresses with age/HIV duration [134].

HIV-infected individuals, especially as they age, are subject to neuronal Ca^{2+} dysregulation and neurotoxicity elicited by the HIV-1 proteins gp120, Tat, and Vpr [135–137]. Tat protein increases neuronal Ca^{2+} levels via IP3R and NMDAR and L-type Ca^{2+} channels, followed by mitochondrial Ca^{2+} uptake and ROS production, leading to caspase activation and neuronal apoptosis [137–139]. In microglia and astrocytes, Tat and gp120 can interact and trigger the production of cytokines, nitric oxide, and excitotoxins which can intensify the neurotoxic effects of Tat and

gp120 [137]. HIV-1 Vpr is also able to activate the expression of cytokines, ROS, and inflammatory proteins in uninfected and infected cells. Vpr will elicit a slow but persistent elevation of Ca^{2+} leading to glutamate signaling impairment in neuronal cells. Moreover, the calcium homeostasis is disturbed by Vpr via down-regulation of endogenous PMCA [136].

4.4. Inflammation links aging to the brain

The neuroinflammation is present even in the absence of productive infection and may have a different cause, like an undetectable level of virus production, the effects of combination antiretroviral therapy (cART) itself, and/or a chronic and systemic immune action. Together, these factors contribute to HIV-1 neurodegeneration. The stimulated microglia will synthesize neurotoxic molecules, inflammatory mediators like cytokines/chemokines, and provoke glutamate receptor-mediated excitotoxicity, disrupt intracellular calcium concentration and ion channel expression, and mechanisms controlling cAMP levels. Viral latency and residual inflammation are codependent mechanisms promoting each other [140]. The peripheral immune activation and production of peripheral cytokines increase inflammation within the CNS and have been associated with lower cognitive performance [141–148].

In the HIV-infected brain, the microglia will produce NF-kappa B, triggering the secretion of the pro-inflammatory cytokine TNFα which stimulates NF-kappa B signaling in neurons of the medial basal hypothalamus in a feed-forward loop. IKKβ/NF-κB inhibits GnRH and activates aging-related hypothalamic GnRH degeneration. The inhibition of IKKβ/NF-κB activation or GnRH treatment can reverse the aging effects of HIV-1 and increase the lifespan [149]. This feedback loop has been linked to the hypothalamic programming of systemic aging [149]. In primary astrocytes, HIV stimulates C3 expression indirectly, via NF-κB-dependent induction of IL-6, which will activate the C3 promoter [150].

A senescence-associated secretory phenotype (SASP), a central aspect of cellular senescence, is activated when the certain chemokines/cytokines, especially IL-6, IL-8, and IL-1 α, are secreted. These interleukins play a major role in brain aging [151–153]. HIV-1 infection is quickly followed by the inflammasome activation, allowing the release of IL-6, IL-8, IL-18, IFN-γ, IL-1β, IL-2Rα, IL-3, IL-6, TNFα, IL-1Rα, IL-10, IL-1α, and TNFβ [154, 155].

4.5. Influence of cART on neurotoxicity

The development of highly active antiretroviral therapy (HAART) has changed the neurodegeneration pattern and prevented the major cognitive impairments of AIDS, increasing survival times.

To be effective in the brain, combination antiretroviral therapy (cART) has to cross the blood–brain barrier and be metabolized. However, if these drugs made it possible to alleviate cognitive impairment, they can contribute to it and damage nerve cells. Indeed, long-term cART can generate toxic effects and contribute to HAND. The efavirenz (EFV) metabolites 7-hydroxyefavirenz (7-OH-EFV) and especially 8-hydroxyefavirenz (8-OH-EFV) can provoke damage to dendritic spines. Furthermore, the 8-OH-EFV metabolite can trigger calcium flux in neurons, mainly mediated by L-type voltage-operated calcium channels (VOCCs), and acts as a potent neurotoxin [156]. The mitochondrial respiratory capacity (SRC) is reduced by maraviroc, raltegravir, lopinavir, darunavir, zidovudine, emtricitabine, abacavir, nevirapine,

and efavirenz but not by indinavir. Efavirenz and maraviroc provoke a reduction of ATP at the synapse that may contribute to its dysfunction [157, 158]. Additionally, the non-nucleoside reverse transcriptase inhibitor efavirenz can decrease neural stem cell proliferation [159]. Non-nucleoside reverse transcriptase inhibitors (NRTIs) are key players in HAART-induced mitochondrial toxicity due to their capacity to inhibit the DNA polymerase in charge of the synthesis of mitochondrial DNA, Pol-γ [160–162]. Some brains under HAART present neuroinflammation combined with mononuclear phagocyte activation, notably in the hippocampus, and can reach the level seen in AIDS and HIVE pre-HAART [163].

4.6. Anti-oxidant defense

Oxidative phosphorylation is a highly efficient way of generating energy to produce adenosine triphosphate (ATP). Oxygen is a key player in this metabolic pathway in mitochondria to break down the glucose. Reactive oxygen species (ROS), hydroxyl radical (OH$^-$), hydrogen peroxide (H$_2$O$_2$), and superoxide (O$_2^-$) are usually produced at low levels. If the balance between antioxidants and pro-oxidant is disturbed, oxidative damage can occur, followed by mitochondrial dysfunction and accumulation of cytotoxins leading to cell death. The brain is rich in fatty acids, which make neurons highly sensitive to oxidative alteration and peroxidation [164], in particular because it has fewer antioxidants than other tissue and higher iron levels. Under oxidation, the membrane lipids can undergo lipid peroxidation producing malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). The endogenous brain defense against oxidative stress is composed of glutathione peroxidase (GPx1), superoxide dismutases (SOD), catalase, and glutathione (γ-l-glutamyl-l-cysteinylglycine, GSH) [165].

In HAND, oxidative stress increased levels of oxidized proteins and lipid peroxidation products, at the same time than a deficit in GSH and GPx1 [166–169]. The lipid peroxidation induced by HIV-1 affects the specific region of the brain [170] and is correlated with the gravity of HAND [171]. Several viral proteins are involved in this mechanism. Tat is inducing the reactive oxygen species (ROS) superoxide (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$), increasing at the same time the levels of lipid peroxidation. It is able also to induce nitric oxide synthase (iNOS) to generate nitric oxide (NO), which when combined with superoxide (O$_2^-$) will form the peroxynitrite (ONOO) [172]. Gp120 triggers the release of arachidonic acid in glial cells [173], from the lipoxygenase and cyclooxygenase pathways [173]. Gp41 can provoke neuronal cell death by a mechanism involving NO formation, iNOS, and a deficit in glutathione, which will subsequently disrupt the mitochondrial function [174, 175]. Vpr induces the production of ROS after a reduction in the total GSH/GSSG ratio and an increase in the level of oxidized glutathione (GSSG) [176].

4.7. Mitochondria

In the mitochondrial theory of aging (or free-radical theory of aging), the reactive oxygen species, which are the products of respiration, damage the membranes, mitochondrial DNA (mtDNA), and proteins, causing an accumulation of cellular and molecular injuries subsequently responsible for aging. It creates a "vicious cycle" when the mtDNA damage increases ROS production, which will damage even more the mtDNA [177].

The HIV-1 infection initiates changes in mitochondrial electron transport chain (ETC), mitochondrial trafficking proteins, glycolytic pathways, and proteins implicated in several energy pathways. In the presence of HIV-1 proteins, the mitochondria face a higher energy demand, will consume more oxygen, and show a higher capacity to produce ATP. These mechanisms are usually observed when there is cellular damage leading to ROS production [178].

During HAND, mitochondrial fission/fusion mechanism is dysregulated. The mitochondrial fission protein (dynamin 1-like, DNM1L) is decreased in frontal cortex tissues of HAND patients, and the soma of damaged neurons presents elongated and enlarged mitochondria. The GFAP-gp120 mice present the same phenotype, and gp120 also decreases the DNML1 levels. The mitochondrial fusion seems to be the predominant mitochondrial dynamic in the brains of HAND patients [179]. HIV-1 Tat provokes a massive diminution in the mitochondrial membrane potential, a mechanism closely linked to fusion and fission. It is probably the consequence of the quick increase Tat caused on the intracellular Ca^{2+}, whether via the NMDA receptor or L-type calcium channels. The levels of mitochondrial fission protein Drp1 are consequently increased and the mitochondrial morphology is altered by Tat. Unbalanced mitochondrial fission and fusion are responsible for several neurodegenerative disorders [180]. HIV-1 Vpr promotes the formation of permeability transition pores in mitochondria, which disturbs the transmembrane potential and the ATP synthesis. This process permeabilizes the mitochondria and allows the release of cytochrome c via a cascade of caspase and leads to apoptosis [181]. Moreover, Vpr decreases rapidly the mitochondrial membrane potential [182], which provokes the formation of the permeability transition pore complex (PTPC) [183], composed by the adenine nucleotide translocator (ANT) on the inner mitochondrial membrane and the voltage-dependent anion channel (VDAC) on the outer mitochondrial membrane. This creation of mitochondrial conductance channels will allow the release of apoptosis-inducing factor cytochrome c into the cytoplasm, as described in striatal and cortical neurons of rats [184]. Following HIV-1 Vpr treatment, the intracellular glutathione is reduced, maybe the result of decreased ATP availability when Vpr binds to the ANT on the inner mitochondrial membrane [185]. HIV-1 Vpr is also described to impair the mitochondria axonal transport [186].

4.8. Autophagy

Defects in autophagy can lead to several neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS) for the most common [187]. Without autophagic cleaning, protein aggregates will accumulate and become toxic to the cells. Aging is slowing down the efficiency of cell autophagy (macroautophagy and chaperone-mediated autophagy) either by diminishing the autophagic flux or by too much cargo accumulation from chronic cell injury [187]. Some interventions intend to increase the autophagy levels like caloric restriction or autophagy-inducing drugs can attenuate age-linked pathologies and lengthen the lifespan [188–190].

The activation of autophagy is beneficial for the virus during the initial phase of HIV-1 infection in many cell types [191]. However, the autophagy inhibition is necessary for virus replication in later phases of infection, stimulating the biogenesis of exosomes enclosing viral products [192]. In HIV-1 dementia, the neurodegeneration seems to be associated with the

inhibition of neuronal autophagy, a decrease in autophagy-inducing protein, and an increase in sequestosome-1/p62 [193]. Autophagy genes like *SQSTM1*, *ATG5*, and *LAMP1* appear to be differentially regulated at the transcriptional, translational, and post-translational levels by HIV-1 in the brain at a different stage of the disease [194]. Basal autophagy is inhibited by the HIV-1 infection in CD4+, monocyte/macrophage lineage [195], as well as in neurons and astrocytes and leads to neuro-glial toxicity [196].

Nef binds BECN1 and inhibits the proteolytic stages of autophagy in HIV-infected macrophages [197, 198]. In astrocytes, Nef is also blocking the fusion of autophagosome to lysosome to escape the viral degradation, increasing LC3II and p62/SQSTM1 levels. It is interesting to note that LC3 and Gag interact and that basal autophagy promotes optimal Gag processing and yields of HIV in macrophages [195]. Gag processing is increased when autophagy is induced, manipulating the autophagy process to maximize the viral replication in infected macrophages. The Gag protein is the main target of autophagy, but HIV-1 has taken advantage of Gag targeting for its replication, especially in macrophages. HIV-1 Tat is targeted for degradation via an ubiquitin-independent pathway, as an anti-HIV effect, interacting with p62/SQSTM1 in CD4+ T lymphocytes. However, Tat can counteract this degradation by decreasing the quantity of the autophagy markers LC3II andp62/SQSTM1 coupled with the membrane in neurons [199]. Moreover, Tat can bind to the lysosomal-associated membrane protein 2A (LAMP2A) to regulate the fusion of autophagosomes with lysosomes. Through this interaction with LAMP2, Tat may allow abnormal autophagolysosome formation, leading to neurodegeneration [199]. Gp120 on the opposite is inducing autophagy in neuronal cells [200], probably as a protective mechanism from the toxic effects of gp120 [201].

5. Conclusion

The aging mechanism linked to aging is the consequence of multiple heterogeneous processes and is the interplay of several areas including physiological changes, metabolical aging, or cognitive impairment. The HIV-associated aging is distinct from chronological aging and should be treated as well. It will be influenced by the cognitive reserve of the patient, modeled by its social, cultural, physical, and economic environment.

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