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CHAPTER THREE

HIV in the cART era and the mitochondrial: immune interface in the CNS

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Contents

Abstract

HIV-associated neurocognitive disorders (HAND) persist in the era of effective combined antiretroviral therapy (cART). A large body of literature suggests that mitochondrial dysfunction is a prospective etiology of HAND in the cART era. While viral load is often suppressed and the immune system remains intact in HIV+ patients on cART, evidence suggests that the central nervous system (CNS) acts as a reservoir for virus and low-level expression of viral proteins, which interact with mitochondria. In particular, the HIV proteins glycoprotein 120, transactivator of transcription, viral protein R, and negative factor have each been linked to mitochondrial dysfunction in the brain. Moreover, cART drugs have also been shown to have detrimental effects on mitochondrial function. Here, we review the evidence generated from human studies, animal models, and in vitro models that support a role for HIV proteins and/or cART drugs in altered

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production of adenosine triphosphate, mitochondrial dynamics, mitophagy, calcium signaling and apoptosis, oxidative stress, mitochondrial biogenesis, and immunometabolism in the CNS. When insightful, evidence of HIV or cART-induced mitochondrial dysfunction in the peripheral nervous system or other cell types is discussed. Lastly, therapeutic approaches to targeting mitochondrial dysfunction have been summarized with the aim of guiding new investigations and providing hope that mitochondrial-based drugs may provide relief for those suffering with HAND.

1. Introduction

Human immunodeficiency virus (HIV) associated neurological disorders remain prevalent despite the advent of combined antiretroviral therapy (cART), with as high as 50% of HIV+ patients being afflicted in both the pre- and post-cART eras (Ellis et al., 2010; Gabbai, Schmidt, Castelo, Oliveira, & Lima, 1990; Grant et al., 1992; Heaton et al., 2010, 2015). HIV-associated neurocognitive disorders (HAND) affect approximately 50% of patients on cART and have devastating consequences for patients and their families (Heaton et al., 2010, 2015). HIV-associated sensory neuropathy (SN) is the most common HIV-associated neurological disorder with over 50% of HIV+ individuals being affected (Ellis et al., 2010). This review will focus on mitochondrial dysfunction as an underlying mechanism of HAND in the cART era. Studies on the pathogenesis of HIV-SN may also provide clues into the neuropathogenesis of HIV and cART, and therefore will be discussed when deemed relevant and insightful.

While the etiology of HAND is likely multifactorial, depending on both genetic and environmental factors, mitochondrial dysfunction has long been implicated in HIV-associated neurological disorders, whether the disorders manifest in the central nervous system (CNS) or in the peripheral nervous system (PNS) (Estanislao, Thomas, & Simpson, 2004; Gabbai et al., 1990; Simpson, Chin, Keilbaugh, Lin, & Prusoff, 1989) in pre- and post-cART eras. Neuropathological analyses of human tissues, animal models for HAND and in vitro models for HIV-induced neurotoxicity have shown that HIV, HIV proteins produced by infected cells and ART can all compromise the function of neuronal mitochondria. Some of the first work identifying alterations in mitochondria during HIV infection investigated muscle biopsies from cART naïve HIV+ patients as well as patients on at least one ART drug (Dalakas, 2001; Dalakas, Semino-Mora, & Leon-Monzon, 2001; Gabbai et al., 1990; Lewis & Dalakas, 1995). Later work

using human samples and clinical data used pharmacogenetic approaches to identify genetic and risk factors for ART-mediated mitochondrial neurotoxicity. Using animal models for ART-induced neurotoxicity, it was discovered that some ART drugs, specifically the d-drugs (stavudine, didanosine, zalcitabine), disrupted mitochondrial DNA (mtDNA) synthesis and integrity (Lewis & Dalakas, 1995). In part because of this off-target effect, these drugs are no longer used in clinical practice. Later studies found alterations to mitochondrial related markers in the brains of HIV+ patients on cART, although the mechanisms of ART-induced neurotoxicity are not completely understood and also likely depend on genetic and environmental factors. To study the contribution of HIV and HIV proteins to HAND, rodent models were developed that expressed HIV proteins in the brain (Kim et al., 2003; Mucke, Masliah, Rockenstein, & Toggas, 1993; Villeneuve et al., 2016). Others have developed "humanized" mice that allow for HIV-infection to be recapitulated in vivo. The most relevant, and most costly, models for HIV-infection involve simian immunodeficiency virus (SIV) infection of rhesus macaques, which have provided additional evidence for mitochondrial dysfunction as a pathogenic mechanism in HIV-SN (Lehmann, Chen, Borzan, Mankowski, & Hoke, 2011). However, SIV-induced mitochondrial dysfunction in the CNS has not been explored. In vitro cellular models have also been valuable tools to help understand the roles of ART drugs, HIV, and specific HIV proteins in mitochondrial dysfunction during HAND. Finally, the most recent evidence from the HIV field, and studies of other neurodegenerative diseases such as Alzheimer's disease, have revealed evidence that inflammatory stimulation of bystander and immune cells can compromise the bioenergetic capacity of mitochondria in neurons and thereby cause neurotoxicity. These mechanisms of mitochondrial dysfunction, as well as the potential targeting of mitochondria as a therapeutic strategy in HAND, will be discussed throughout this review.

1.1 HIV neuropathogenesis in pre- and post-cART eras

The neuropathological correlates of HAND have changed drastically since the widespread use of cART. Prior to the advent of cART, the neuropathogenesis of HIV was characterized by giant multinucleated cells, white matter myelin pallor and marked loss of neuronal dendrites and synapses (Gray et al., 1994; Masliah, Miller, & Terry, 1993). While the rate of HAND diagnosis changed little with the widespread use of cART, HIV associated

dementia (HAD) was much more prevalent in the pre-cART era (Heaton et al., 2015). In patients on cART regimens, those with HAND are more likely to be diagnosed with milder forms of neurocognitive impairment (NCI) (Heaton et al., 2015). In the cART era, the neuropathology is less severe and neurotoxicity may be caused by a combination of low-level viral replication, viral protein production, cART drugs, and chronic inflammation (Gelman, 2015; Gelman et al., 2012; Levine et al., 2016). While evidence showed mitochondrial dysfunction may have contributed to HIV-associated PNS dysfunction in the pre-cART era, there was little evidence of alterations in CNS mitochondrial function. Examination of tissues from HIV-infected decedents on cART identified alterations in markers for mitochondrial function and abnormal mitochondria in neurons of the CNS and PNS as a common characteristic of HIV-associated neurological disorders. Investigations utilizing animal models and in vitro cellular models for HIV- and ART-associated neurological disorders have vastly increased our understanding of how mitochondrial dysfunction may play a role in HAND and HIV-SN in the cART era. Generally, two theories of the etiology of HAND and HIV-SN remain: (1) the direct model in which HIV, HIV-proteins, or ART directly alter mitochondrial function in neurons; and (2) the indirect model, in which bystander cells that have been infected, activated or damaged by HIV, HIV proteins, or ART disrupt mitochondrial function in neurons. In this review, we will focus on evidence of mitochondrial dysfunction during the cART era by surveying clinical features of HIV-associated neurological disorders and the published neuropathological studies of mitochondria in human tissues from decedents on cART. Next, we will focus on studies of HIV-induced mitochondrial dysfunction as well as cART-induced mitochondrial dysfunction and how these mechanisms may underlie HIV-associated neurological disorders. Lastly, we will propose the next steps to understanding mitochondrial dysfunction in the CNS during the cART era and how these steps may lead to novel therapeutics that target mitochondrial dysfunction in the CNS.

1.2 HAND clinical features

HAND describes a clinical diagnosis of cognitive impairment in HIV+ individuals. To make a diagnosis of HAND, HIV+ patients undergo a comprehensive neuromedical evaluation that includes assessment of medical history, structured medical and neurological examinations, and the collection of blood, cerebrospinal fluid (CSF), and urine samples (Heaton et al., 2010;

Woods et al., 2004). Clinical data (plasma viral load [VL], postmortem interval, CD4 count, global, learning and motor deficit scores [GDS, LDS, and MDS]) are also collected.

HAND diagnosis is determined via a comprehensive neuropsychological test battery, which was constructed to maximize sensitivity to neurocognitive deficits associated with HIV infection. Raw test scores are transformed into demographically adjusted T-scores, including adjustments for age, education, gender and race. These demographically adjusted T-scores are converted to clinical ratings to determine presence and degree of NCI in seven neurocognitive domains (Woods et al., 2004). As part of the neuropsychological battery, participants complete self-report questionnaires of everyday functioning: the Lawton and Brody Activities of Daily Living questionnaire, (Lawton & Brody, 1969), and/or the Patient's Assessment of Own Functioning (PAOFI; Chelune & Baer, 1986; Chelune, Heaton, & Lehman, 1986). Participant's performance on the neuropsychological test battery and their responses to the everyday functioning questionnaires are utilized to assign one of three HAND diagnoses following established criteria (Antinori et al., 2007). These three categories are HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).

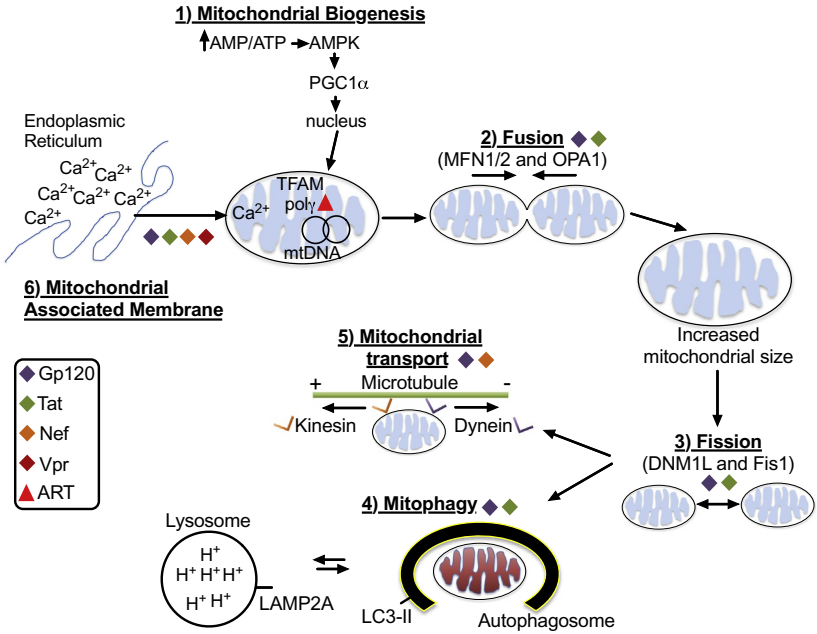
The overall rate of HAND diagnoses did not change significantly with the widespread use of cART. However, the characteristics of HIV infection and the severity of HAND did change drastically. Pre-cART HAD diagnoses were around 30%, while ANI and MND made up the other 20% of all HIV-infected individuals with HAND. After cART implementation, HAND still affects an estimated 15–50% of HIV+ persons, with the lowest prevalence in those started on cART early after initial infection and with sustained viral suppression on ART. HAND persists despite improved clinical characteristics compared to the HIV+ patients in the pre-cART era, such as reduced viral load, increased CD4+ cell count, and decreased co-morbidities. However, studies of CSF and postmortem brain tissues from HIV+ patients in the post-cART era reveal that certain neuropathological markers persist. For example, distinct HIV quasispecies isolated from the CSF of virally suppressed patients suggests that the CNS can act as viral reservoir in patients on suppressive cART (Dahl et al., 2014; Ferretti, Gisslen, Cinque, & Price, 2015; Lescure et al., 2013). Imaging studies of the brains of HIV+ infected persons on cART also suggest persisting injury related to HIV infection (Ances et al., 2010; Ances, Ortega, Vaida, Heaps, & Paul, 2012). Neurocognitive outcomes often correlate with nuclear and

mitochondrial DNA (mtDNA) sequences and interactions between the two in certain populations. Neuropathological studies of postmortem brain tissues from HIV+ decedents on cART that were diagnosed with HAND reveal reduced neuronal integrity, astrogliosis, microgliosis, increased expression of inflammatory cytokines and alterations in mitochondrial morphology and integrity (Avdoshina et al., 2016; Fields, Serger, Campos, et al., 2015; Gelman et al., 2012; Solomon et al., 2017; Soontornniyomkij et al., 2018). It is likely that HAND neuropathogenesis is multifactorial, including host and viral genetics as well as environmental variables. Mitochondrial dysfunction may be a common pathway in HAND and therefore a promising therapeutic target.

1.3 Mitochondrial dysfunction in neurological disorders

Mitochondria are the powerhouse of the cell due to their role in transforming bioenergetic substrate into usable energy in the form of ATP. It is now clear that these organelles are also involved in cell signaling activities, stress responses, apoptosis and likely many other important cellular events that are responsible for providing neurons with energy substrates. It is not surprising that alterations in mitochondrial activity, quantity, mass, recycling and distribution are hallmarks of many brain diseases as the high energy demand of neurons makes them particularly dependent on a reliable source of energy. Multiple mechanisms of neurotoxicity appear to be at work among individuals with HAND, including HIV activation of apoptotic pathways (Kaul, Garden, & Lipton, 2001), dysregulation of calcium (Ca^{2+}) homeostasis (Gendelman, Lipton, Tardieu, Bukrinsky, & Nottet, 1994; Nath et al., 2000), mitochondrial dynamics, and oxidative stress (Nath, 2002; Norman et al., 2008). All of these potentially neurotoxic processes can be buffered by a healthy pool of mitochondria.

To maintain and enrich the pool of healthy mitochondria, cells operate tightly regulated processes for generating (biogenesis) and transporting new mitochondria, while degrading damaged mitochondria by a process called mitophagy (Ventura-Clapier, Garnier, & Veksler, 2008) (Schematic 1). According to bioenergetic needs, healthy mitochondria are split (mitochondrial fission) and distributed throughout the soma, dendrites, and axons to fuel synapses used for learning, memory and other crucial brain functions (Nikoletopoulou & Tavernarakis, 2014; Ventura-Clapier et al., 2008). Damaged portions of the mitochondrial network are tagged for degradation and then split from healthy mitochondria (more fission) to be recycled by mitophagy. Disruption of mitochondrial biogenesis, mitochondrial



Schematic 1 HIV and cART disruption of mitochondrial processes. (1) Mitochondrial biogenesis is stimulated when energy demands are not being met, which increases the ratio of AMP:ATP. AMP activates AMPK, which in turn phosphorylates many signaling factors including PGC-1α. PGC-1α enters the nucleus where it, along with other transcription factors (TF), binds to DNA to produce many mRNAs including TFAM, a TF involved in mtDNA replication and gene expression. Some ART drugs interfere with mtDNA replication, leading to damaged mtDNA. (2) Mitochondrial fusion requires, among other proteins, MFN1, MFN2, and OPA1. HIV proteins gp120 and Tat are involved in alterations in mitochondrial fusion. (3) Mitochondrial fission requires, among other proteins, DNM1L and Fis1. HIV proteins gp120 and Tat are involved in alterations in mitochondrial fission. (4) Damaged mitochondria (red) are tagged for removal and engulfment by LC3-II-positive autophagosomes, which then fuse to lysosomes to form autophagolysosomes in a process termed mitophagy. HIV gp120 and Tat have been shown to alter autophagy and mitophagy in neurons and Tat also alters mitophagy in microglial cells. (5) To be transported throughout the cell, mitochondria are linked to adaptor proteins and molecular motors, dynein and kinesin, which drag the mitochondria along microtubules. HIV gp120 alters mitochondrial transport. (6) The mitochondrial associated membrane (MAM) is a region of the endoplasmic reticulum that is in contact, via multiple proteins, to the mitochondrial network. At the MAM, proteins, lipids, and Ca^{2+} are delivered to mitochondria. The MAM is implicated in mitochondrial toxicity due to increased Ca^{2+} by way of HIV gp120, Tat, Nef, and Vpr.

transport and/or mitophagy is implicated in several neurodegenerative diseases including Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and HAND (Bonavia et al., 2001; Fields, Dumaop, Eleuteri, et al., 2015; Fields et al., 2013; Fields, Serger, Campos, et al., 2015;

Huang, Chiang, Lin, Chiou, & Chow, 2012; Kitayama et al., 2008; McArthur, Steiner, Sacktor, & Nath, 2010; Repunte-Canonigo et al., 2014; van der Walt et al., 2003; Wang et al., 2013; Ye, Tai, & Zhang, 2012). Below, we discuss these regulatory mechanisms in more detail.

1.3.1 Mitochondrial alterations in HIV+ brains from the cART era

Mitochondrial dysfunction in the brain during HAND is supported by direct and indirect evidence ranging from brain imaging studies in HIV+ patients to neuropathological assessments of postmortem brain specimens. HIV enters the brain early during infection, causing inflammation and neurodegeneration, which likely increases the metabolic needs of neurons and glia (Gendelman et al., 1994; Koenig et al., 1986). Some cART drugs also penetrate the brain parenchyma and studies from the PNS have shown that these compounds can have profound effects on mtDNA replication and integrity (Ene, Duiculescu, & Ruta, 2011; Lewis & Dalakas, 1995). Kinases active in the cell can act on nucleoside reverse transcriptase inhibitors (NRTI) through phosphorylation steps that generate nucleotide reverse transcriptase inhibitors, which can then enter mitochondria and compete with native nucleotides at DNA polymerase active sites and thereby inhibit mtDNA replication via chain termination. Direct evidence for HIV and cART-induced mitochondrial dysfunction in the brain includes measures of mitochondrial related biomarkers and direct visualization of mitochondria in postmortem brain specimens. Some of the first evidence for HIV and cART-induced mitochondrial dysfunction in the brain showed reduced levels of *N*-acetylaspartate in the white matter of HIV+ patients taking didanosine and/or stavudine (Schweinsburg et al., 2005). Surprisingly, no significant changes were found in the gray matter of these patients. Neuropathological studies showed accumulation of mtDNA damage in the frontal cortex of HAND patients (Zhang et al., 2012), which has implications for the processes of mitochondrial biogenesis and ATP production. A recent study found similar markers of mitochondrial damage in a cohort of HIV+ brains that were stratified by use of methamphetamine (Var et al., 2016). In this study, increased mitochondrial injury in Brodmann area 46 of frontal cortices was associated with worse neurocognitive function in HIV+METH− individuals (Var et al., 2016). Two additional studies by the same group showed that cell-free mitochondrial DNA in CSF is associated with viral rebound, inflammation, and severity of HAND diagnosis (Perez-Santiago et al., 2016) and also with HIV replication, iron transport and mild HAND (Mehta et al., 2017). Other studies of postmortem brain

tissues showed alterations in autophagy, which is required for efficient recycling of mitochondria, in brains of HIV+ patients with HIVE or HAND diagnoses (Alirezaei, Kiosses, & Fox, 2008; Fields et al., 2013). Consistent with recycling of mitochondria, proteins that promote mitochondrial fission, DNML1 and Fis 1, were found to be reduced while proteins that promote mitochondrial fusion, MFN1 and optic atrophy (OPA) 1, were found to be increased in HAND brains compared to HIV+ brains from decedents that had no diagnosed impairment (Avdoshina et al., 2016; Fields, Serger, Campos, et al., 2015). Another study using the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort found that certain mtDNA haplogroups were associated with reduced risk for HAND in Hispanics (Hulgan et al., 2015). A study investigated 1025 patients in the CHARTER cohort to characterize the interplay of mtDNA haplogroup and nuclear genetic associations to HAND status (Smieszek et al., 2018). The patients were stratified by ethnicity as being either of European-descent, African-descent, or admixed Hispanic. This study revealed interactions between nuclear SNPs and mtDNA haplogroups that confer susceptibility to NCI within the European- and African-descent groups (Smieszek et al., 2018). This study also revealed an interaction between rs978490 and haplogroup T, which alters the expression of POLG2, a subunit of the mtDNA polymerase γ (Smieszek et al., 2018). Collectively, these findings suggest that mitochondrial DNA replication, integrity and dynamics play a strong role in HAND. Questions remain as to how alterations in mtDNA affect mitochondrial biogenesis and contribute to HAND, how mitochondrial function and dynamics are affected in different brain cell types and the interplay between these cells downstream of dysfunctional mitochondria.

Indirect evidence for mitochondrial dysfunction in HAND during the cART era includes the presence of features that are involved in mitochondrial dysfunction in related neurodegenerative diseases such as AD and PD. For example, amyloid beta (Aβ) accumulation, a hallmark of Alzheimer's disease, has been associated with HIV infection of the brain during the cART era (Ortega & Ances, 2014). Moreover, receptors and cellular processes that are involved in clearing Aβ from the brain are altered in HAND brains (Fields et al., 2018). Aβ is associated with altered mitochondrial biogenesis, mitochondrial fission/fusion, mitophagy and increased oxidative stress through generation of ROS. In support of Aβ-induced mitochondrial dysfunction in the brain during HIV infection, Green et al. reported Aβ accumulation as a common pathologic feature of HIV infection (Green et al., 2005). Later, Achim et al. reported increased levels of Aβ in HIV brain

tissue, specifically neurons (Achim, Adame, Dumaop, Everall, & Masliah, 2009). Aβ is associated with increased astrogliosis and altered bioenergetics in neurons (Jiang & Cadenas, 2014; Yin, Sancheti, Patil, & Cadenas, 2016) through a mechanism that could plausibly be active in HIV-infected brains. Triggering receptor on myeloid cells 2 (TREM2) plays an important role in clearing Aβ from the brain and alterations in TREM2 expression is associated with HIV and AD (Fields et al., 2018; Gisslen et al., 2019). Regardless of the stimuli, whether it be Aβ, cART, HIV, age, or a combination of factors, glial-mediated inflammation persists in HIV+ brains in the cART era, and may appropriate energy substrate that is needed by neurons (Jiang & Cadenas, 2014; Yin et al., 2016).

2. HIV proteins and mitochondrial dysfunction in the CNS

Even in the era of cART, HIV replication and low-level expression of HIV proteins in the brain and periphery and the ensuing inflammatory response are likely to underlie many of the neuronal complications associated with HIV-infection (Ko et al., 2018; Levine et al., 2016; Tso et al., 2018). While cART has reduced viral load in the periphery, instances of distinct virus isolated from CSF (viral escape) and antibodies against HIV proteins found in the brain provide evidence of low-level viral replication and HIV protein expression in brains of patients on ART (Ferretti et al., 2015; Levine et al., 2016; Mukerji et al., 2018). While high levels of HIV replication in the brain are not detectable in the cART era, antibodies for HIV proteins and HIV genomic DNA have been found in CSF and in brains of HIV+ decedents that were on cART (Bachani, Sacktor, McArthur, Nath, & Rumbaugh, 2013; Ko et al., 2018; Tso et al., 2018). HIV proteins, such as transactivator of transcription (Tat), glycoprotein (gp) 120, viral protein (VP) R, and negative factor (Nef) have been linked to immune activation, oxidative stress, altered mitochondrial transport, altered autophagic flux, induction of apoptosis, Ca^{2+} signaling, and neurotoxicity (Bansal et al., 2000; Dinkins, Arko-Mensah, & Deretic, 2010; Nath, Conant, Chen, Scott, & Major, 1999; Nath, Padua, & Geiger, 1995; Piller, Jans, Gage, & Jans, 1998; Rozzi, Avdoshina, Fields, & Mocchetti, 2018; Sawaya, Khalili, Mercer, Denisova, & Amini, 1998; Teodorof-Diedrich & Spector, 2018; Thangaraj et al., 2018; Valcour & Shiramizu, 2004). The involvement of HIV proteins in mitochondrial dysfunction in the brain was highlighted in a study that

found alterations in the electron transport chain (ETC), glycolytic pathways, mitochondrial trafficking proteins and proteins crucial to various energy pathways in a rat model for HIV-induced neurotoxicity (Villeneuve et al., 2016).

2.1 Gp120

Glycoprotein 120 (gp120) makes up the tripartite spike of the viral envelope that is essential for viral infection. On the surface of virions, gp120 is non-covalently linked to the membrane-spanning gp41. Upon binding to CD4 and a chemokine co-receptor (CCR5 or CXCR4) on the host cell, gp120 facilitates fusion of the viral and host cell membranes and deposition of the viral capsid into the cytoplasm (Deng et al., 1996). Antagonists of gp120 binding and the fusion process inhibit HIV infection (Scarlatti et al., 1997).

Gp120 was one of the first HIV proteins shown to be toxic. Although neurons do not express CD4, they express both CCR5 and CXCR4, through which gp120 in the picomolar range induces neurotoxicity in vitro (Bachis, Major, & Mocchetti, 2003; Lipton, Sucher, Kaiser, & Dreyer, 1991; Meucci & Miller, 1996). Other studies have shown that gp120 enters the cytoplasm through multiple mechanisms and can bind directly to cellular machinery and induce neurotoxicity (Berth, Caicedo, Sarma, Morfini, & Brady, 2015). A transgenic (tg) mouse model that expresses gp120 in astrocytes via the glial fibrillary acidic protein (GFAP) promoter showed evidence of neurotoxicity and neuropathological features that resemble those observed in the brains of HAND decedents, such as simplified neuronal processes (Toggas et al., 1994) and loss of dendritic spines (Bachis, Wenzel, Boelk, Becker, & Mocchetti, 2016). More recent subcellular neuropathological examination and functional assays of in vitro and in vivo models have revealed that gp120 has profound effects on neuronal mitochondrial dynamics, mitophagy, and apoptosis (Avdoshina et al., 2016; Fields et al., 2013; Pandhare, Dash, Jones, Villalta, & Dash, 2015; Shah, Kumar, Simon, Singh, & Kumar, 2013; Teodorof-Diedrich & Spector, 2018).

2.1.1 Gp120 and mitochondrial dynamics

Recent studies using in vitro and in vivo models have shown that gp120 can have robust effects on mitochondrial fission/fusion and transport in neurons. Aside from receptor-mediated neurotoxicity, gp120 can be internalized by PNS and CNS neurons (Bachis et al., 2003; Berth et al., 2015). Once inside the neuronal cytoplasm, gp120 binds to neuronal specific tubulin β III and is transported both anterogradely and retrogradely and alters the transport of

mitochondria in neuronal processes (Avdoshina et al., 2016). Another study found that rat neurons exposed to gp120 recombinant protein or to conditioned media from monocyte derived macrophages that were exposed to gp120 exhibited impaired movement of mitochondria (Meeker, Poulton, Clary, Schriver, & Longo, 2016). These gp120-induced alterations in mitochondrial transport could explain the dendritic simplicity and neurotoxicity observed in gp120 tg mice and neurons in vitro (Bennett, Rusyniak, & Hollingsworth, 1995; Lipton, Brenneman, Silverstein, Masliah, & Mucke, 1995; Mucke et al., 1993; Savio & Levi, 1993; Toggas et al., 1994).

Altered mitochondrial morphology has been reported in the brains of HAND decedents including abnormally elongated mitochondria, damaged cristae, reduced levels of the mitochondrial fission proteins DNM1L and Fis1 and increased levels of the mitochondrial fission protein MFN1 (Avdoshina et al., 2016; Fields, Serger, Campos, et al., 2015). Exposing differentiated SH-SY5Y neuroblastoma cells and primary rat neurons to recombinant gp120 also produced reductions in DNM1L protein levels and enlarged mitochondria, both of which are reversed after transduction with lentivirus that overexpressed DNM1L (Fields, Serger, Campos, et al., 2015). Similar findings were observed in the mouse model for HIV-induced neurotoxicity that expresses gp120 in the brain (Avdoshina et al., 2016; Fields, Serger, Campos, et al., 2015; Toggas et al., 1994). Lentiviral-mediated gene delivery of DNM1L to the brain of gp120 tg mice reversed the mitochondrial damage, mitochondrial elongation, gliosis, and neurodegeneration (Fields, Serger, Campos, et al., 2015). In a follow-up study using the anti-inflammatory drug FK506 (tacrolimus) both gliosis and neurodegeneration, but not the mitochondrial alterations, were ameliorated in gp120 tg mice. These findings suggest that the gp120-induced mitochondrial alterations may produce neurodegeneration through proinflammatory pathways (Fields et al., 2016). However, not all studies on gp120 show the same results regarding mitochondrial fission and fusion. A recent study reported that gp120 enhanced mitochondrial fission (Teodorof-Diedrich & Spector, 2018). These differences may be due to different experimental models. However, that would not explain the elongated mitochondria that were observed in neuropathological studies of brain tissues from HIV+ decedents diagnosed with HAND (Avdoshina et al., 2016; Fields, Serger, Campos, et al., 2015). Due to the importance of distributing mitochondria throughout the cytoplasm of cells, gp120-induced alterations in mitochondrial fission/fusion and transport may provide a promising therapeutic target in HIV+ patients with neurological disorders.

2.1.2 Gp120 and mitophagy

Gp120 was first shown to be associated with altered autophagy in the GFAP-gp120 tg mouse model, in which the levels of protein markers for autophagy (LC3, Beclin1, and Cathepsin D) were reduced in tg mice compared to wild-type littermates (Fields et al., 2013). As mentioned in the section above on mitochondrial dynamics, mitochondrial fission was also found to be reduced in the gp120 tg mice. Although, the effects on mitophagy have not been assessed in these mice, these findings suggest that reduced autophagy and reduced mitochondrial fission may synergistically contribute to the elongated and damaged mitochondria observed in the brains of these animals (Avdoshina et al., 2016; Fields, Serger, Campos, et al., 2015). Another study in SH-SY5Y neuroblastoma cell culture found that gp120 induced activity of proline oxidase (POX), a mitochondrial inner membrane metabolic enzyme that catalyzes the first step of proline catabolism (Pandhare et al., 2015). This study also showed that markers for autophagy were increased in SH-SY5Y cells along with increased ROS levels, each of which were reversed by treating the cells with a competitive inhibitor of POX (Pandhare et al., 2015). The authors concluded that POX and autophagy were induced as a stress response to gp120-induced neurotoxicity (Pandhare et al., 2015). In light of the effects of gp120 on DNM1L levels and mitochondrial fission (Avdoshina et al., 2016; Fields, Serger, Campos, et al., 2015), it is likely that mitophagy is also affected in these cells. The most recent study on gp120 and mitophagy showed that gp120 induced mitochondrial fragmentation but only incomplete mitophagy in primary human neuroglial cultures (Teodorof-Diedrich & Spector, 2018). Interestingly, and somewhat contradictory to previous studies, this study also showed that gp120 and Tat had similar effects on neuronal mitochondrial dynamics and autophagy, by increasing mitochondrial fission and increasing accumulation of LC3. The authors of this interesting study concluded that while the prerequisites of mitophagy were increased by gp120 and Tat, the delivery of mitochondria to the lysosome was impaired, leading to incomplete mitophagy (Teodorof-Diedrich & Spector, 2018). The discrepancies between studies may reflect use of different model systems, ranging from mouse in vivo to mouse, rat, and human in vitro models for gp120-induced neurotoxicity.

2.1.3 Gp120 effects on Ca^{2+} signaling and apoptosis

Through binding chemokine receptors CCR5 and CXCR4, gp120 induces apoptotic pathways in neurons (Kaul et al., 2001). Activation of these

pathways leads to progressive reduction in mitochondrial membrane potential and release of Ca^{2+} from the endoplasmic reticulum (Haughey & Mattson, 2002), increased oxidative stress (Mattson, Haughey, & Nath, 2005), and recruitment of the pro-apoptotic transcription factor p53 (Garden et al., 2004). Gp120 induces caspase-3 proteolytic activity and mitochondrial release of cytochrome *c* and cell death in neuronal cultures (Garden et al., 2002). This gp120-induced apoptosis was blocked by specific inhibitors of both the Fas/tumor necrosis factor-alpha/death receptor pathway and the mitochondrial caspase pathway (Garden et al., 2002). Direct treatment of rat neurons with gp120 recombinant protein or with conditioned media from gp120-treated monocyte derived macrophages resulted in delayed accumulation of Ca^{2+} and decreased Ca^{2+} clearance from the cell which was associated with dendritic beading, a sign of neurotoxicity (Meeker et al., 2016). This toxicity was reversed by a p75 neurotrophin receptor agonist (Meeker et al., 2016). These findings show that gp120 can directly impact how mitochondria regulate important signaling pathways and cell death in neurons.

2.2 Tat

Tat first was shown to induce inflammation and oxidative stress in non-neuronal cells (Venkatesh, Arens, Subramanian, & Chinnadurai, 1990; Westendorp et al., 1995). However, the ability of Tat to induce inflammation and neurotoxicity was also observed early in the epidemic (Sabatier et al., 1991). As it became clear that neuronal dysfunction persisted despite reduced peripheral viral load in patients on cART, investigators became more interested in how Tat affects CNS neurons.

HIV Tat, a trans-activator of transcription for viral replication, is one of the first viral genes expressed by infected cells upon integration of proviral DNA into the genome of the host cell. Tat is released from infected lymphoid cells (Ensoli et al., 1993), monocytic cells (Turchan et al., 2001) and glial cells (Tardieu, Hery, Peudenier, Boespflug, & Montagnier, 1992), including astroglia (Tornatore, Chandra, Berger, & Major, 1994; Tornatore, Meyers, Atwood, Conant, & Major, 1994). Tat has been linked to activation of, and inflammatory gene expression by microglia and astroglia as well as mitochondrial alterations in microglia, astroglia, and neurons (Rozzi et al., 2018; Teodorof-Diedrich & Spector, 2018; Thangaraj et al., 2018). In HIVE brains from the pre-cART era, Tat was detected in the brains of patients using immunohistochemical methods

(Del Valle et al., 2000; Hudson et al., 2000). More recently, in brains from patients that were on cART, Tat-specific antibodies were detected in the CSF by a sensitive ELISA (Bachani et al., 2013). Hence, Tat cytotoxicity and pro-inflammatory capacity likely persist in some HIV+ persons despite adherence to viral suppressive cART regimens. HIV Tat alters mitochondrial integrity, morphology, dynamics, signaling and recycling in neurons, but also inflammation, oxidative stress, and mitochondrial function in glia, which sets the stage for neuroinflammation that persists in a reservoir of low-level HIV infection.

2.2.1 Tat and mitochondrial dynamics

Mitochondrial dynamics and mitophagy are closely linked as proper mitochondrial fission is a prerequisite of mitophagy. HIV-Tat impacts mitochondrial dynamics and mitophagy via direct interactions with mitochondria and through interactions with associated proteins, though data are conflicting. Some of the first evidence for Tat affecting mitophagy came from studies that showed Tat-induced alterations in neuronal lysosomes. Lysosomal ability to pump protons was impaired by Tat, which affects lysosomal size, degradative activity, and fusion to autophagosomes (Hui, Chen, Haughey, & Geiger, 2012). Tat also binds directly to lysosomal associated membrane protein 2 (LAMP2) in neuronal cells and in the brain of transgenic mice expressing Tat from astroglia (Fields, Dumaop, Eleuteri, et al., 2015). This interaction between Tat and LAMP2A was shown to alter lysosomal fusion to autophagosomes in neurons (Fields, Dumaop, Eleuteri, et al., 2015). The effects of Tat were reversed by rapamycin, which has been shown to reverse inflammation and mitochondrial alterations in other models (Fields, Dumaop, Eleuteri, et al., 2015). While these studies do not show direct interactions with mitochondria, they do provide evidence for impairment in the process of recycling mitochondria through mitophagy, which requires functional lysosomes and autophagosomes. Recent studies have shown that Tat also alters mitophagy, though the findings were not always consistent with previous studies, possibly due to the use of different model systems, dose, and time of exposure to Tat.

Mitochondrial fission is a prerequisite of mitophagy, as damaged portions of mitochondria are pinched apart through the action of the GTPase DNM1L. HIV-Tat promotes CDK5 localization to the cytoplasm of neurons and causes hyperphosphorylation of tau (Fields, Dumaop, Crews, et al., 2015). Interestingly, overexpression of tau leads to mitochondrial elongation and dysfunction via DNM1L mislocalization (DuBoff, Gotz, & Feany, 2012).

Tat also impairs mitochondrial fission and reduces the average diameter of neuronal mitochondria (Rozzi et al., 2018). Tat may function differently in microglia than in neurons by increasing expression of proteins associated with mitophagy such as PINK1, PRKN, and DNM1L, but still inhibiting mitophagy by blocking functional autophagy (Thangaraj et al., 2018). The most recent study showed that Tat promotes mitochondrial fission and incomplete mitophagy in human neurons (Teodorof-Diedrich & Spector, 2018).

2.2.2 Tat and mitophagy

Tat protein was first shown to affect lysosomes in neurons, which could directly affect autophagy and hence mitophagy. Further support for Tat-mediated effects on autophagy were observed in the doxycycline-inducible GFAP-Tat tg mouse model and in mouse primary neurons. In this study, it was shown that Tat binds to LAMP2 and alters lysosomal fusion to the autophagosome (Fields, Dumaop, Eleuteri, et al., 2015). These findings are consistent with the more recent study in which Tat was found to induce incomplete mitophagy by inhibiting the delivery of the damaged mitochondria to the lysosomal compartment in human neuroglial cultures (Teodorof-Diedrich & Spector, 2018). Together, these findings provide strong evidence that Tat affects neuronal autophagy. Tat was also recently shown to induce defective mitophagy in microglia (Thangaraj et al., 2018). Using mouse primary microglial cells, it was found that Tat altered mitochondrial membrane potential and induced the mitophagy signaling proteins PINK1, PRKN, and DNM1L as well as the autophagy proteins, BECN1, LC3 and SQSTM1 (Thangaraj et al., 2018). These data suggest that the impact of Tat on autophagy and mitophagy may not be cell specific, whereas the responses may be cell specific.

2.2.3 Tat effects on Ca^{2+} signaling and apoptosis

Tat induces apoptosis through activation of caspases, calcium overload and oxidative stress (Kruman, Nath, & Mattson, 1998). Recombinant Tat induced apoptosis and increased mitochondrial membrane potential associated with retraction of neurites in rat cortical neurons (Perry et al., 2005). A few years later, mechanistic studies in neuronal cultures showed that Tat acts by binding ryanodine receptors on mitochondria (Norman et al., 2008). These Tat-mediated direct insults to mitochondria should be viewed within the context of the other mechanisms of Tat-induced neurotoxicity including altered autophagy and mechanisms acting through NMDA receptors. Tat was shown to potentiate glutamate toxicity through

phosphorylation of the NMDA receptor in hippocampal neurons causing Ca^{2+} efflux (Haughey, Nath, Mattson, Slevin, & Geiger, 2001). Tat also inactivates cytochrome *c* and induces permeabilization in mitochondria isolated from mouse brains (Lecoeur et al., 2012). Using cortical neurons isolated from mouse brains, Tat induced mitochondrial permeabilization and increased ROS. However, the mitochondrial permeabilization was reversed by exposing the neurons to creatine (Stevens, Gawryluk, Hui, Chen, & Geiger, 2014). As indicated by a mouse model for Tat-induced neurotoxicity, Tat has devastating effects on neurons and collectively, these studies suggest that Tat-induced alterations in mitochondria are likely a causative factor (Kim et al., 2003).

2.3 Vpr and Nef

Vpr and Nef are less well-studied HIV proteins compared to gp120 and Tat. However, they have been shown to elicit profound effects on CNS mitochondria. Vpr is packaged in the viron and is important for initial infection of CD4+ T cells and macrophages (Kogan & Rappaport, 2011). Nef plays a role in maintaining a persistent state of HIV infection by promoting the survival of infected cells through down modulation of cell-surface receptors at the immune synapse (Chaudhry et al., 2005; Das & Jameel, 2005). Both Vpr and Nef disrupt mitochondrial function in uninfected CNS cells in vitro and in vivo, implicating them in HIV-induced neurological dysfunction.

2.3.1 Vpr and mitochondrial dynamics

Several studies support a role for Vpr in disrupting mitochondrial dynamics and transport along axons, which may accelerate neurodegeneration and neuronal aging. Though not shown in neurons, it was shown that Vpr associates with the mitochondrial associated membrane of HEK293 cells and inhibits expression of MFN2 resulting in small and damaged mitochondria (Huang et al., 2012). It is plausible that a similar mechanism occurs in the CNS. Vpr accumulates in mitochondria, binds to adenine nucleotide translocator, reduces mitochondrial membrane potential, reduces ATP production and inhibits mitochondrial transportation in primary mouse neurons (Kitayama et al., 2008). In a recent study using primary mouse neurons, Vpr was found to reduce the amount of mitochondrial movement along axons through association with the adenine nucleotide translocator (Kitayama et al., 2008; Wang et al., 2017). These alterations were associated with an increase in biomarkers of aging (Kitayama et al., 2008;

Wang, Walaas, Sihra, Aderem, & Greengard, 1989). Another study found RNA transcripts for Vpr in brains of HIV+ patients (Jones et al., 2007). This group also found that soluble Vpr caused neuronal apoptosis through cytochrome *c* release, p53 induction, and activation of caspase 9 (Jones et al., 2007).

2.3.2 Vpr effects on Ca^{2+} and apoptosis

Vpr was shown to induce apoptosis in several cell types before investigations began to determine the effects of Vpr on neuronal Ca^{2+} signaling and apoptosis (Jacotot et al., 2000; Patel, Mukhtar, Harley, Kulkosky, & Pomerantz, 2002). In neurons, Vpr causes release of cytochrome *c*, which results in Ca^{2+} release from ER, and activation of caspases (Jones et al., 2007).

2.3.3 Nef effects on apoptosis

Nef induced the expression of caspase-3 in cultured human astrocytes, leading to dose-dependent cell death (Acheampong et al., 2009). In a mouse model of hyperglycemia, Nef induced production of caspase-3, ROS, and inflammatory genes (Acheampong et al., 2009). In primary human brain microvascular endothelial cells, Nef induced the expression of multiple caspases and apoptosis related genes. Nef has been shown to alter Ca^{2+} signaling through interactions with the IP_3 receptor in T cells, but this mechanism has not yet been observed in neurons (Manninen & Saksela, 2002). Based on these findings, Nef has the potential to induce cytotoxicity in multiple types of CNS cells and may be a promising target for therapeutic intervention (Acheampong et al., 2005).

2.4 HIV proteins and mitochondrial mediated oxidative stress

While oxidative stress in the periphery during HIV-infection has been well studied, we will focus on HIV-protein-related oxidative stress in the CNS. As mentioned above in the section on mitophagy, gp120 increased the levels of ROS in neuroblastoma cells by increasing activity of POX, a metabolic enzyme located in the mitochondrial inner membrane (Pandhare et al., 2015). Multiple studies have linked gp120 to increased oxidative stress, but few have investigated the role of mitochondria in these processes, and those that do, rarely assess CNS cells (Price, Ercal, Nakaoke, & Banks, 2005; Ronaldson & Bendayan, 2008; Shah et al., 2013). Tat-induced oxidative stress occurs concomitant with increased ATP production and mitochondrial membrane potential in rat cortical neurons. However, this study did not link increased oxidative stress directly to mitochondria and

these changes required high concentrations (2 μg/mL) of Tat (Perry et al., 2005). Recombinant Nef also increased production of ROS in human astrocytes and in a mouse model of diabetes (Acheampong et al., 2009). Despite the paucity of data supporting the idea that HIV-proteins directly cause mitochondrial-mediated increases in oxidative stress in the CNS, we hypothesize that such deleterious mechanisms are at work in some cases and require further studies.

2.5 HIV proteins and immunometabolism

Several studies indicate that upon activating glial cells, HIV proteins induce metabolic and inflammatory responses (Jiang & Cadenas, 2014; Lee, Wollam, & Olefsky, 2018; Van den Bossche, O'Neill, & Menon, 2017; Yin et al., 2016). The metabolic responses include alterations in ROS, ATP production, lactate production, oxygen consumption and autophagic flux. These metabolic changes precede, or are concomitant with, induction of inflammatory gene expression (Lee et al., 2018; Natarajaseenivasan et al., 2018; Van den Bossche et al., 2017). This is consistent with a growing body of evidence indicating that increased activation of glial cells compromises the bioenergetic substrate pool available to neurons and thereby limits neuronal bioenergetic capacity (Jiang & Cadenas, 2014; Yin et al., 2016). Moreover, microglia, the macrophages of the brain, require shifts in metabolic pathways to orchestrate immune signaling, which is thought to determine the inflammatory state in the brain (Lee et al., 2018; Van den Bossche et al., 2017). Regarding immunometabolic shifts in astroglia, a recent study showed that Tat induced alterations in human astrocytes occurs concomitant with changes in oxygen consumption, ATP production, and lactate production (Natarajaseenivasan et al., 2018). Moreover, these shifts in metabolism were associated with neurotoxicity (Natarajaseenivasan et al., 2018). The HIV protein Nef has been shown to induce the expression of inflammatory cytokines in astrocytes (Liu & Kumar, 2015) and in separate studies, Nef was shown to alter autophagy in astrocytes (Saribas, Khalili, & Sariyer, 2015), suggesting a link between the metabolic pathway and the immune response of activated astroglia. Another study using primary mouse microglia showed that Tat induces alterations in mitochondrial function, mitochondrial fission and mitophagy concomitant with increases in inflammatory gene expression (Thangaraj et al., 2018). Together, these studies suggest that HIV proteins induce immunometabolic mechanisms in activated astroglia and microglia. In light of studies from other neurodegenerative diseases such as AD

(Jiang & Cadenas, 2014; Yin et al., 2016), there is strong evidence that the chronic activation of glial cells in HIV-infected persons could contribute to the bioenergetic deficiencies and mitochondrial abnormalities observed in CNS neurons in HAND patients in the cART era.

3. cART and mitochondrial dysfunction in the CNS

Early after the advent of antiretroviral drugs, alterations in mitochondrial function were identified in neurons. However, most studies involved PNS neurons and were associated with HIV-SN. The nature of cART-induced mitochondrial dysfunction in the PNS is likely not identical to that of the CNS. Still, studies from the PNS may provide clues as to how cART could alter mitochondria in the brain and impede neurocognitive function. Moreover, pharmacogenetic studies from the PNS and CNS likely have widespread implications since the nuclear and mtDNA are the same, save for somatic mosaicism (Freed, Stevens, & Pevsner, 2014) and mutation, in every organ of the body. We will therefore discuss findings from the PNS that support cART-induced mitochondrial dysfunction in the context of the findings in the CNS of HAND brains and studies utilizing cellular models for the CNS. We will also cover the limited evidence that cART is affecting mitochondrial function in the CNS. These studies include pharmacogenetics utilizing DNA and cognitive outcomes from large cohorts of HIV+ patients and in vitro models.

3.1 Post-cART era human studies

Initial studies determined that ART drugs that inhibit the reverse transcriptase required for HIV replication also altered the function of human mtDNA polymerase γ and damaged mtDNA (Lim & Copeland, 2001; Martin, Brown, Matthews-Davis, & Reardon, 1994). One study detected HIV-SN in up to 30% of HIV+ patients that were taking 2′3-dideoxyctidine (ddc), a non-azylated dideoxynucleoside analog used to treat AIDS (Dalakas et al., 2001). Using nerve specimens from HIV+ patients with ddc-neuropathy compared to HIV+ patients with neuropathy but never exposed to ddc (Dalakas et al., 2001), axonal degeneration was apparent in all HIV+ samples. However, abnormal and enlarged mitochondria, excessive vacuolization, electron-dense structures and myelin degeneration were associated with ddc exposure in axons and Schwann cells (Dalakas et al., 2001). A later study isolated blood cells from 24 HIV−controls, 47 HIV+asymptomatic patients who had never been treated with cART,

and 8 HIV+ patients who received cART nucleoside analogs and had hyperlactatemia (Cote et al., 2002). The ratio of mitochondrial DNA copies to nuclear DNA was reduced in HIV-infected patients with symptomatic, nucleoside-related hyperlactatemia, but this resolved after discontinuation of therapy (Cote et al., 2002). These studies provide evidence that some cART RT inhibitors alter mtDNA integrity and replication, and hence may affect mitochondrial biogenesis (Lehmann et al., 2011). The effects of cART on mitochondria in the CNS remain unexplored.

3.1.1 Pharmacogenetics of cART and mitochondrial dysfunction

Mitochondrial DNA sequence variability is associated with variable risk for developing HAND and HIV-SN. A case-control led investigation of Adult AIDS Clinical Trials Group (ACTG study 384) and of ACTG Human DNA Repository participants, which included 509 total HIV+ subjects, revealed that mitochondrial haplogroup T was an independent predictor of NRTI-associated peripheral neuropathy (Hulgan et al., 2005). A separate study of 250 self-identified white, non-Hispanic HIV+ patients reported that mitochondrial 4918G polymorphism was associated with increased risk for cART-associated peripheral neuropathy (Canter et al., 2008). These associations remained after controlling for age, baseline CD4 count, plasma HIV RNA level, and NRTI randomization. Another recent study by the same authors sequenced and analyzed the genome of 384 non-Hispanic black persons from the ACTG study and found that 33% developed peripheral neuropathy. Multivariate analyses showed that mtDNA subhaplogroup L1c was an independent predictor of neuropathy (Canter et al., 2010). This was the first study showing that an African mtDNA subhaplogroup may increase risk for HIV-SN. These studies show that mtDNA sequence may interact with cART, HIV, and environmental factors to alter mitochondrial, and ultimately neuronal, function.

Several mutations in nuclear genes have also been associated with increased susceptibility for developing HIV-SN. Interestingly, the protein products of these genes have direct or indirect connection to the function of mitochondria. An investigation of 509 HIV+ participants from the ACTG 384 study and ACTG Human DNA Repository specimens were randomized to receive three or four drug antiretroviral therapy with didanosine (ddI) plus stavudine (d4T) or zidovudine plus lamivudine, given with efavirenz, nelfinavir, or both, with up to 3 years of follow-up. This study found that the C282Y mutation in the hemochromatosis gene were associated with a reduced risk of HIV-SN during antiretroviral therapy

(Kallianpur et al., 2006). A recent publication found that polymorphisms in the genes *P2X4R* and *CAMKK2* are associated with susceptibility to HIV-SN, possibly through increased production of tumor necrosis factor-alpha (Gaff et al., 2018). While at first glance this study may not arouse suspicion of mitochondrial involvement, studies in the CNS have shown that inflammatory responses in by-stander cells may utilize energy substrates that would otherwise be used by neuronal mitochondria (Yin et al., 2016). Coupled with the finding that expression of chemokine receptors is increased on cells surrounding cutaneous nerves in patients with HIV-SN (Mountford et al., 2018), infiltrating immune cells that are part of the inflammatory response initiated by TNF-α may compromise mitochondrial function in peripheral neurons. These findings provide additional support for alterations in immunometabolic mechanisms compromising the mitochondrial function and bioenergetic capacity of neurons, albeit in the PNS.

Another study of the CHARTER cohort provided evidence that mtDNA haplogroups have some effect on neurocognitive status in HIV+ individuals (Hulgan et al., 2015). In this study of 1027 HIV+ persons, 72% being on cART regimens, mtDNA haplogroups were assessed along with NCI. Researchers found using multivariate models that haplogroup B mtDNA was associated with less NCI among persons of genetically determined Hispanic ancestry (Hulgan et al., 2015). These findings are particularly interesting considering that overall HIV+ Hispanics have worse NCI compared to Caucasions (Marquine et al., 2018). A more recent study using the CHARTER cohort identified a potential role for interactions between nuclear single nucleotide polymorphisms and mtDNA haplogroups in NCI in HIV+ persons (Smieszek et al., 2018). This study included 1025 HIV+ persons with nuclear and mitochondrial genome-wide genotyping that were assessed for NCI. After assessing how the polygenic effect of SNPs is influenced by mtDNA haplogroups, the study found evidence of a significant interaction between the nuclear SNPs *en masse* and mtDNA haplogroups in individuals of European-descent and also in those of African descent (Smieszek et al., 2018). These studies suggest that mtDNA interactions with nuclear DNA and environmental factors may affect mitochondrial function in the brain and also neurocognitive outcomes.

3.2 cART induces mitochondrial toxicity using in vitro models

Protease inhibitors have been associated with oxidative stress in several cell types. A study using SH-SY5Y neuroblastoma cells found that the protease

inhibitors lopinavir and ritonavir induced mitochondrial damage and ROS generation followed by apoptosis (Tricarico et al., 2016). A previous study found that ritonavir protected hippocampal neurons from oxidative stress, but effects on mitochondria were not reported (Wan & DePetrillo, 2002). Using primary rat neurons, efavirenz was found to decrease mitochondrial membrane potential and enhance superoxide production, suggesting damage to the mitochondria (Blas-Garcia et al., 2014). Consistent with these findings, efavirenz induced a dose-dependent decrease in basal and maximal oxygen consumption in neuroblastoma (SH-SY5Y) and glioma (U-251MG) cells (Funes, Blas-Garcia, Esplugues, & Apostolova, 2015). A study by the same group found that efavirenz promotes inducible nitrogen oxide synthase expression in glial cells and thereby alters mitochondrial function (Apostolova et al., 2015). In neurons and glia, efavirenz inhibits mitochondrial ETC complex I, while other complexes are inhibited in neurons after longer exposure to efavirenz (Apostolova et al., 2015). A study focusing on cART drugs with high CNS penetration found that efavirenz, nevirapine, abacavir, emtricitabine, zidovudine, darunavir, lopinavir, raltegravir, or maraviroc caused a reduction in spare respiratory capacity in mitochondria isolated from striatal nerve terminals of male Long-Evans rats (Stauch, Emanuel, Lamberty, Morsey, & Fox, 2017). In yet another study, tenofovir disproxil fumarate, efavirenz, ritonavir, and atazanavir were all found to reduce mitochondrial membrane potential in rat primary neurons, though these changes did not correlate with neurotoxicity (Robertson, Liner, & Meeker, 2012). Collectively, these studies suggest that cART, while extending the life of HIV+ persons, may contribute to mitochondrial dysfunction in the CNS of HAND patients.

4. Preventing HIV-induced mitochondrial toxicity

The advent of cART has reduced the severity of HAND but has done little to alter the prevalence of this HIV-associated comorbidity. The benefit of cART likely stems from reduced viral load in the periphery and in the CNS, which also reduces the amount of toxicity produced by HIV proteins, HIV replication, and the accompanying inflammatory responses. Unfortunately, the mitochondrial related neurotoxicity of cART drugs as well as the low-level viral replication that occurs in virally suppressed patients represents an unmet need for viable therapeutics. Clinical trials have produced underwhelming results. Studies using in vitro and in vivo models for

HIV-induced neurotoxicity may offer clues for developing therapeutic strategies to target mitochondria in HIV+ individuals on cART.

Antioxidants have been shown to reduce neuronal apoptosis in in vitro neuronal models for HIV-induced neurotoxicity (Agrawal, Louboutin, Reyes, Van Bockstaele, & Strayer, 2006; Pocernich, Sultana, Mohmmad-Abdul, Nath, & Butterfield, 2005; Rozzi et al., 2014; Turchan et al., 2003). Since mitochondria are a major producer of oxidative stress, especially dysfunctional mitochondria, the use of antioxidants may be therapeutic to HAND or HIV-SN patients. The immunophillin FKBP51 is a mitochondrial protein that protects cells against oxidative stress (Gallo, Lagadari, Piwien-Pilipuk, & Galigniana, 2011), and its expression is increased in the brains of HIV+ individuals (Tatro et al., 2009). FK506, a molecule already approved for clinical use, binds immunophillins and has shown promising effects in reducing HIV gp120 associated neurodegeneration and restoring mitochondrial homeostasis in the gp120 tg mouse model for HIV-induced neurotoxicity (Fields et al., 2016). Creatine has been shown to promote maintenance of ATP levels, protect mitochondrial membrane potential, reduce oxidative stress and be neuroprotective in neurons exposed to Tat protein (Stevens et al., 2014). Consistent with these findings, blocking uptake of Tat by heparan sulfate and dextran sulfate reduced mitochondrial dysfunction in neurons (Chauhan et al., 2003).

Mitochondrial dynamics and mitophagy may present pathways that can be targeted for therapeutic approaches in HIV+ individuals. Delivery of the mitochondrial fission gene *DNML1* to the brain of the gp120 tg mouse model reduced neuroinflammation and neurodegeneration, suggesting that molecules that enhance mitochondrial fission may be protective against gp120 neurotoxicity (Fields, Serger, Campos, et al., 2015). Rapamycin, another clinically-approved drug, was shown to enhance autophagy and reduce both neurodegeneration and neuroinflammation in a tg mouse model that expresses the Tat protein in the brain (Fields, Dumaop, Eleuteri, et al., 2015).

Brain derived neurotrophic factor (BDNF) has been shown to be neuroprotective by supporting mitochondrial health. A flavonoid found in chocolate and green tea, epicatechin, is able to reduce Tat-induced mitochondrial dysfunction in neurons, possibly through increasing BDNF expression (Nath, Bachani, Harshavardhana, & Steiner, 2012). BDNF also protects neurons exposed to gp120 (Bachis et al., 2003). There is evidence that BDNF enhances mitochondrial biogenesis, mitochondrial transport, and mitochondrial metabolism in the brain (Cheng et al., 2012; Marosi & Mattson, 2014; Su, Ji, Sun, Liu, & Chen, 2014). Despite these

promising observations, some studies suggest that BDNF signaling can be neurotoxic in the brain (Bachis et al., 2016; Bredesen & Rabizadeh, 1997; Singh et al., 2008; Yang et al., 2014). Nevertheless, neurotrophic factors such as BDNF deserve further exploration as therapeutic agents in HIV+ individuals.

Therapeutic interventions for mitochondrial dysfunction in antiretroviral toxic neuropathy have been tested with limited success. Acetyl-L-Carnitine (ALC) is crucial for normal mitochondrial function as it acts as an acetyl-group donor in high-energy metabolism and is a transport molecule for free fatty acids (Bremer, 1990). ALC showed promising therapeutic efficacy in animal models of diabetic neuropathy (Sima et al., 1996) as well as immunological benefits in HIV infection (Scarpini, Sacilotto, Baron, Cusini, & Scarlato, 1997). In patients with antiretroviral toxic neuropathy, ALC improved cutaneous nerve density and was associated with clinical benefits (Hart et al., 2004). However, ALC was unsuccessful in alleviating HIV DSP symptoms in a small open-label study involving 20 patients (Osio et al., 2006) and in a randomized, placebo-controlled trial of 90 patients (Youle, 2007). A later open-label, single-arm study showed improvements in subjective measures of pain whereas changes were not observed in measures of IENF density or mtDNA levels, providing little objective support for use of ALC (Valcour et al., 2009).

Immunometabolic mechanisms in activated glia may represent a novel therapeutic avenue for HAND. Evidence from neurodegenerative diseases with strong inflammatory signatures in the brain, such as AD, suggests that reducing activation of infected or uninfected glia may reduce mitochondrial dysfunction in neurons (Jiang & Cadenas, 2014; Yin et al., 2016). Immunometabolic mechanisms in microglia and astroglia are likely playing a role in HAND and related mitochondrial dysfunction (Fields et al., 2018; Natarajaseenivasan et al., 2018; Van den Bossche et al., 2017). Hence, therapies that reduce activation of glia may support mitochondrial function in neurons. Cannabinoid receptor agonists have been shown to be neuroprotective in animal models for chronic neuroinflammation and HIV-induced neurotoxicity and also inhibit inflammatory gene expression in glial cells (Aguirre-Rueda et al., 2015; Avraham et al., 2013; Benard et al., 2012; Lu et al., 2008; Marchalant, Cerbai, Brothers, & Wenk, 2008; Marchalant, Rosi, & Wenk, 2007; Martin-Moreno et al., 2012; Sheng et al., 2005). Moreover, cannabinoid receptor 1 is localized to mitochondria and may represent a novel therapeutic target in HAND (Navarrete & Araque, 2008; Navarrete, Diez, & Araque, 2014; Robin et al., 2018).

The one-size-fits all method of prescribing pharmaceuticals was clearly not productive for HIV+ individuals as many different regimens are used to different levels of success, not only in different individuals but also during different times of the infection. A more personalized medicine approach may also be useful in combating HAND. As pharmacogenetics studies have illustrated, the genetics of the HIV+ individual can play a role in HIV and cART interactions and cognitive outcomes. Environmental factors such as culture, socioeconomic status or geography may also play a role in how HIV or cART affects mitochondrial function, neurotoxicity and cognitive outcome (Fields et al., 2018; Marquine et al., 2018; Rubtsova et al., 2018). Hence, methods to identify personalized treatments involving in vitro assays that utilize the patients own cells could increase effectiveness of cART while also reducing interactions with different mtDNA sequences and thereby reduce neurotoxicity. For example, a study showed that cART can accelerate aging of mitochondria by clonal expansion of mutated mtDNA (Payne et al., 2011). Fibroblasts from patients with mitochondrial diseases are used to identify deleterious mechanisms and similar methods may provide insights for personalized treatments for HAND (Ryan et al., 2018). Studies of HIV and cART-induce mitochondrial dysfunction using cell models generated from HIV+ patients could provide such an avenue for treating HAND.

Mitochondrial biogenesis is disrupted in multiple neurodegenerative diseases. Yet no studies, to our knowledge, have investigated this process as a causative factor in HAND. Mitochondrial biogenesis is linked to metabolic signaling pathways such as mitochondrial dynamics, autophagy and the AMPK pathway (Nikoletopoulou & Tavernarakis, 2014; Uittenbogaard & Chiaramello, 2014). The transcriptional regulators of mitochondrial biogenesis are altered in brains of AD and HD patients and increasing mitochondrial biogenesis by gene delivery methods can be neuroprotective (Onyango, 2018; Sheng et al., 2012; Tsunemi et al., 2012; Uittenbogaard & Chiaramello, 2014). Stimulating mitochondrial biogenesis in neurons may represent a novel therapeutic for HAND and this approach also deserves further investigation.

5. Conclusion

Even with the widespread implementation of effective cART, HAND remains highly prevalent and mitochondrial dysfunction appears to play a major role. As the HIV+ population continues to age on long-term cART, all evidence suggests that disorders of the CNS will only increase.

As the lifespan of HIV+ individuals increase, comorbidities of aging may also synergize with those caused by low-level viral replication and neurotoxicity of cART drugs. The data presented in this review suggest that mitochondria, not only in neurons, but also in glia, may represent a promising target for reducing HAND in the cART era.

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