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REVIEW

Human Immunodeficiency Virus Promotes Mitochondrial Toxicity

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Abstract Combined antiretroviral therapies (cART) have had remarkable success in reducing morbidity and mortality among patients infected with human immunodeficiency virus (HIV). However, mild forms of HIV-associated neurocognitive disorders (HAND), characterized by loss of synapses, remain. cART may maintain an undetectable HIV RNA load but does not eliminate the expression of viral proteins such as trans-activator of transcription (Tat) and the envelope glycoprotein gp120 in the brain. These two viral proteins are known to promote synaptic simplifications by several mechanisms, including alteration of mitochondrial function and dynamics. In this review, we aim to outline the many targets and pathways used by viral proteins to alter mitochondria dynamics, which contribute to HIV-induced neurotoxicity. A better understanding of these pathways is crucial for the development of adjunct therapies for HAND.

Keywords $Ca2^{+}$ · gp120 · HAND · Mitochondria · Neurotoxicity · Tat

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Introduction

Human immunodeficiency virus type-1 (HIV) infection continues to be a global health problem. In addition to infection and depletion of T cells, HIV rapidly enters the central nervous system (CNS) where it productively infects macrophages, microglia (Dunfee et al. 2006; Janssen et al. 1989), and to some extent astrocytes (Conant et al. 1994; Eugenin et al. 2011). The presence of the virus leads to progressive cognitive impairments in a large subset of infected individuals. Even with the advent and implementation of combined antiretroviral therapy (cART) to diminish HIV viral load, over 50% of HIV patients in the USA develop HIV-associated neurocognitive disorders (HAND) that range from asymptomatic to severe dementia (Clifford and Ances 2013; Nightingale et al. 2014). Behaviorally, HAND is characterized with executive dysfunction and memory impairments, with significant impairments in attention, multitasking, and judgment, as well as memory encoding and retrieval (Saylor et al. 2016). One of the hallmark neuropathological features most correlating with these cognitive deficits in HAND is synaptodendritic damage, particularly decreased synaptic and dendritic density (Ellis et al. 2007; Masliah et al. 1997). These neuropathological indices are also confirmed in rodent models of HAND by showing significant neuronal atrophy accompanied by disruption to neuronal function (Bachis et al. 2016; D'Hooge et al. 1999; Toggas et al. 1994). However, the mechanisms by which HIV damages the CNS remain obfuscated considering that microglia but not neurons are infected.

Postmortem brains of HIV-positive individuals with cognitive alterations exhibit signs of impaired mitochondrial metabolism (Bennett et al. 2014; Opii et al. 2007). In addition, when compared to HIV-positive with no cognitive alterations, HAND brains contain mitochondria with abnormal morphology (Avdoshina et al. 2016a; Fields et al. 2016), including the

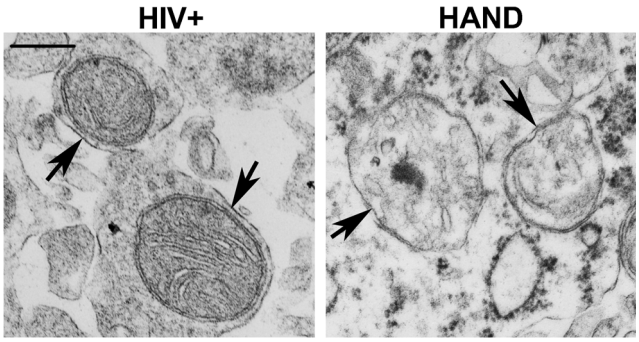

Fig. 1 Neuronal mitochondria in HAND display disrupted cristae. Cortical sections from HIV+ subjects with no cognitive alterations and HAND subjects were analyzed by transmission electron microscopy (TEM) as previously described (Avdoshina et al. 2016a) to visualize mitochondria. Please note that mitochondria (arrows) in HAND exhibit loss of well-defined cristae (bar = 1 μM). Magnification ×25,000

lack of integrity of inner membrane cristae (Fig. 1). This scenario is similar to that observed in other neurological diseases such as Alzheimer's disease in which mitochondrial ultrastructure is altered in such a way that cristae are disrupted (Reddy and Reddy 2011). Mitochondria play a role in neuronal survival through a variety of metabolic mechanisms (Mattson et al. 2008), Ca^{2+} homeostasis and the reduction of reactive oxygen species (ROS), among them. In addition, mitochondria control the production of high-energy intermediates, such as ATP. Neurons are highly energetically dependent and require ATP at distant regions such as axonal and dendritic synapses, linking their function and survival tightly with ATP production (Berthet et al. 2014; Dickey and Strack 2011; Merrill et al. 2011). Thus, it is not surprising that mitochondrial dysfunction and disruption of energy production have been proposed to cause neurodegenerative diseases (Burte et al. 2015). The question remains as to how HIV promotes mitochondrial impairment.

Viral Proteins

All HIV-mediated neuronal complications are the consequences of immune activation, oxidative stress, and neurotoxicity that result from either persistent HIV replication in the brain or the release of viral proteins, such as Tat, gp120, and Nef. These proteins are directly toxic to neurons by a variety of mechanisms. In this review, we will be focused on Tat and gp120, as the most neurotoxic viral proteins that promote neuronal injury by altering mitochondrial dynamics.

Tat HIV Tat, a trans-activator of transcription for viral replication, is produced by infected cells once the proviral DNA is formed, and is released from infected lymphoid (Ensoli et al. 1993), monocytic cells (Turchan et al. 2001), and glial cells (Tardieu et al. 1992). Additionally, Tat has been detected in the brains of patients with HIV encephalitis by immunostaining (Del Valle et al. 2000; Hudson et al. 2000) or in the cerebrospinal fluid (CSF) by a sensitive ELISA (Bachani et al. 2013). Thus, Tat expression in the CNS persists despite cART. The expression of Tat is consistent with the view that the brain is a reservoir for HIV.

Tat is one of the HIV proteins with potent neurotoxic activity and various mechanisms of neurotoxicity. Tat induces DNA double strand breaks (Rozzi et al. 2014). This Tat property could be arising from its function as viral transcriptional regulator in the nucleus (Liu et al. 2000; Stauber and Pavlakis 1998). Unrepaired DNA double strand breaks are lethal to cells (Mehta and Haber 2014). Moreover, Tat is also transported along axons and promotes toxicity upon distal sites by traveling through anatomical pathways (Bruce-Keller et al. 2003). However, many of the neurotoxic effects of Tat appear to be mediated by its interactions with cell membrane receptors including the N-methyl-D-Aspartate (NMDA) subtype of glutamate receptors (Eugenin et al. 2007; Haughey et al. 2001; Li et al. 2008). Tat-mediated neuronal injury can be seen at several levels including synaptic and dendritic pruning (Kim et al. 2008), induction of apoptotic cascades (Aksenova et al. 2009), Ca^{2+} dysregulation (Self et al. 2004), and oxidative stress (Aksenov et al. 2003). These neurotoxic effects are not cell specific because in addition to NMDA positive neurons, they are seen in other neuronal populations, including dopaminergic neurons (Bennett et al. 1995; Ferris et al. 2010; Moran et al. 2013).

Gp120 Glycoprotein 120 (gp120) is a part of the viral envelope that is essential for viral infection. It facilitates HIV entry into the host cell by binding to CD4 and the chemokine co-receptors CCR5 and CXCR4 (Deng et al. 1996). Indeed, antagonists of these receptors inhibit HIV infection (Scarlatti et al. 1997).

Much like Tat, the neurotoxic mechanisms are attributed to gp120 are multiple. Neurons do not express CD4, but express both CCR5 and CXCR4. It is widely recognized that gp120, through chemokine receptors, is a potent neurotoxin, promoting neuronal injury in vitro in the picomolar range (Bachis et al. 2003; Lipton et al. 1991; Meucci and Miller 1996). Moreover, mice genetically expressing gp120 (gp120tg) exhibit neuropathological features observed in HAND, such as retracted neuronal processes (Toggas et al. 1994) and loss of dendritic spines (Bachis et al. 2016).

Gp120, after binding to chemokine receptors, activates apoptotic pathways that lead to neuronal dysfunction and loss (Kaul et al. 2001). Such pathways include dysregulation of Ca^{2+} homeostasis (Haughey and Mattson 2002), activation of oxidative stress (Mattson et al. 2005), and induction of the pro-apoptotic transcription factor p53 (Garden et al. 2004). In addition, there are indirect mechanisms that may account for gp120 neurotoxicity. For instance, gp120

enhances blood-brain barrier permeability (Cioni and Annunziata 2002) by acting through downregulation of tight junction proteins, such as zonula occludens (ZO)-1, ZO-2 and occludin (Kanmogne et al. 2005). Gp120 also enhances the expression of matrix metalloproteases 2 and 9, which increase permeability of brain endothelial cells (Price et al. 2005, 2006) and lipid peroxidation in neurons as well as in the vascular endothelium (Louboutin et al. 2010). These changes increased the trafficking of toxic humoral factors, which may contribute to the pathogenesis of HAND.

Viral Proteins and Mitochondria

Tat and gp120 Change Mitochondrial Dynamics HIV promotes mitochondrial-mediated apoptosis of T cells (Grimaldi et al. 2005; Matarrese et al. 2003). However, the discovery that the function (Lehmann et al. 2011; Zhang et al. 2012) and morphology of neuronal mitochondria in HAND subjects are altered (Avdoshina et al. 2016a; Fields et al. 2016) expanded the interest in mitochondrial research in the neuroAIDS field as a possible explanation for causes of neuronal degeneration. Because mislocalization of mitochondria and perturbations to energy production are known to impair neuronal function, and have been linked to neurodegenerative diseases (Burte et al. 2015), we will review some of the overwhelming evidence that points at impaired mitochondrial dynamics/function as an important contributor for HIV-induced neurotoxicity.

Tat and gp120 appear to exert a differential effect on mitochondria, which can be equally deleterious. Tat exposure causes a biphasic increase in mitochondrial membrane potential that is both concentration- and time-dependent (Norman et al. 2007). This increase is linked to significant alterations in synaptic activity, which was surprisingly not found to be due to disruption to mitochondrial distribution, localization, or morphology. Gp120, in contrast, progressively decreased mitochondrial membrane potential (over a time period of 6 h) by mechanisms that could involve excessive release of Ca^{2+} from endoplasmic reticulum, by activation of voltage dependent Ca^{2+} channels (Haughey and Mattson 2002) or increased NMDA trafficking (Xu et al. 2011).

Mitochondria Morphology Important aspects of mitochondria functionality are organelle biogenesis and morphology These occurrences are regulated through mitochondrial fusion and fission (Westermann 2010), which allow mitochondria to fuse together, becoming elongated, or convert into large number of small fragments, respectively. The main mitochondrial fission and fusion proteins are members of the dynamin family, which includes mitofusins (Mfn1–2), dynamin-related protein 1 (Drp1) and optic atrophy 1 (Opa1), each one with a GTPase domain (van der Bliek et al. 2013). Tat and gp120 appear to change the levels and function of some of these proteins, and consequently affect the morphology and number of mitochondria. For instance, the ability of gp120 to increase Mfn1 and Opa1 (Fields et al. 2016) could explain why mitochondria are elongated in neurons exposed to gp120 both in vitro *(*Avdoshina et al. 2016a*)*. Changes in mitochondrial morphology by gp120 are not an in vitro artifact because the cortex of mice expressing gp120 (gp120-tg) under a glial fibrillary acidic protein promoter (Toggas et al. 1994), exhibit elongated mitochondria with broken cristae (Fig. 2). These mice, which display impaired cognitive behavior and pathological features similar to HAND (Toggas et al. 1994), are considered a valid animal model to study the molecular and cellular mechanisms of HIV neurotoxicity. Thus, it should not be surprising that the loss of mitochondrial cristae detected in these mice (Fig. 2) is similar to that observed in HAND (Fig. 1). Moreover, gp120 decreases Fis-1, a mitochondrial outer membrane protein that regulates mitochondrial fission. Downregulation of Fis-1 can lead to progressive elongated mitochondria (Stojanovski et al. 2004) accompanied by early senescence (Yoon et al. 2006). Tat, on the other hand, reduces the size of neuronal mitochondria by a mechanism that appears to either interfere with fusion of damaged mitochondria with healthy one, or to increase fission and inhibit the elimination of damage mitochondria by mitophagy (Rozzi, unpublished). Regardless of which mechanisms are utilized by viral proteins, it is plausible that HIV is neurotoxic by acting on proteins that are important for mitochondrial number and morphology.

HIV Proteins and ATP One of the main functions of mitochondria is to synthetize ATP from dietary sugar or amino acids by ATP-synthase in the electron transport chains (ETC). The ATP produced relies upon an intact and efficient ETC, the activity of four key proteins that make up the redox carrier, named complex I-IV, and the surface area of cristae (Demongeot et al. 2007). The mitochondrial membrane

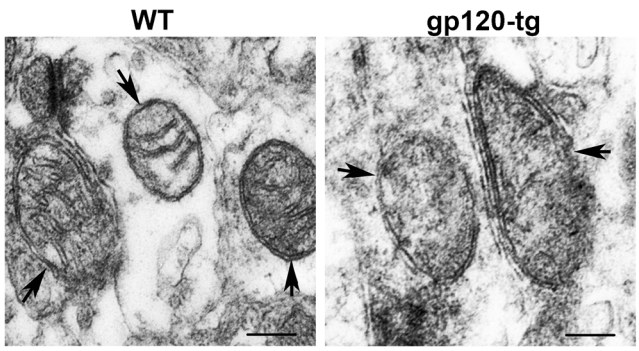

Fig. 2 Viral protein gp120 alters mitochondrial morphology. Mitochondrial morphology was visualized by TEM in cortical sections from wild type (WT) and gp120 transgenic (gp120-tg) mice. Note that mitochondria (*arrows*) in gp120-tg mice display broken cristae. Often, mitochondria in gp120-tg animals are abnormally elongated (bar = 1 μM)

potential ($\Delta\Psi m$) is also critical for the generation of ATP and loss of $\Delta\Psi m$ leads to ATP depletion within the cell thereby contributing to neuronal death (Joshi and Bakowska 2011). Neurons are highly energetically dependent cells as they require as much as 10^4 ATP molecules to transmit a bit at a chemical synapse (Laughlin et al. 1998). Thus, impairment at any step of the ETC or malformed cristae, similar to that described in HIV positive subjects (Avdoshina et al. 2016a), could lead to loss of ATP and the formation of superoxide free radicals. For instance, primary cerebrocortical cells exposed to gp120 exhibit a significant loss of neuronal ATP (Sanchez et al. 2015). This effect could be due to the ability of gp120 to decrease the area of cristae, to block mitochondrial movements, or to increase mitochondrial fusion and thereby inhibit mitophagy (Avdoshina et al. 2016a).

The effect of Tat upon ATP production has conflicting data (Perry et al. 2005; Tiede et al. 2011; Villeneuve et al. 2016), with indications of both increases and decreases in ATP production, in all instances preceding cell death. Nevertheless, the ability of Tat to cause a drastic inhibition of ATP synthase (Lecoeur et al. 2012; Norman et al. 2007) points to a disruption of mitochondrial function. Changes in ETC protein function lead to rapid dissipation of the mitochondrial membrane potential, inhibition of mitochondrial calcium uptake, and release of cytochrome c, a water-soluble component of ETC located within the inner membrane of mitochondria. The release of cytochrome c is a strong indication that apoptosis is activated. Indeed, mitochondria are also involved in the cytochrome c or caspase-dependent death pathway (Garrido et al. 2006; Liu et al. 1996). In contrast, gp120 has been shown to affect both cytochrome c dependent (Garden et al. 2002) and independent apoptosis (Singh et al. 2004). It is important to note that these findings were obtained in cortical and striatal cultures, respectively, suggesting that gp120 may activate different mechanisms of apoptosis depending upon cell types. Regardless of whether Tat and gp120 decrease ATP formation, when Tat or gp120-mediated mitochondrial membrane potential changes are blocked, neurons can be spared from undergoing apoptosis (Lecoeur et al. 2012; Turchan et al. 2001). This consideration indicates that the integrity of mitochondrial function is the key to explaining the neurotoxic properties of Tat and gp120 and that keeping this function intact could be a therapeutic target to improve neuronal survival following HIV infection.

Mitochondrial-Dependent Apoptosis and Ca^{2+} Dysregulation

Mitochondria are essential for buffering intracellular (or cytosolic) free calcium ($[Ca^{2+}]_i$), preventing abnormal elevations in $[Ca^{2+}]_i$ that otherwise would promote a bioenergetic failure of the organelle. High concentrations of Ca^{2+} (and other ions) promote the opening of the permeability transition pore (PTP) located on the mitochondria inner membranes (Bernardi et al. 2015). Prolonged or persistent PTP opening causes mitochondrial depolarization and release of cytochrome c from the mitochondrial intermembrane space. Cytochome c is required for the activation of the initiator of apoptosis, caspase-9, by forming the apoptosomic complex with Apaf-1 (Li et al. 2017). Such complex activates the effector caspase-3 and triggers a feedback loop for mitochondrial disruption through cleavage of anti-apoptotic Bcl-2 family proteins (Chen et al. 2007).

Several HIV proteins have been found to activate key components of PTP opening. Most clearly delineated is the HIV regulatory protein Vpr, which ensures the replication of HIV in infected cells (Schuler et al. 1999). Vpr has been shown to directly target the PTP complex, allowing for the permeabilization of mitochondrial membranes (Jacotot et al. 2000). Additionally, Tat may cause the translocation of Bim, a member of the pro-apoptotic Bcl-2 family, from microtubules to mitochondria, where it induces PTP (Chen et al. 2002). The acute calcium overload caused by Tat can also trigger PTP complex formation. In more recent investigations, Tat was found to have no effect upon Bcl-2 and neither Bax-inhibiting peptide nor Bax channel inhibitor could alter Tat-induced cytochrome c release (Lecoeur et al. 2012). Taken together, these data suggest Tat-induced PTP might be independent of the canonic Bax/Bak-mediated mitochondrial PTP pathway.

Another toxic effect of $[Ca^{2+}]_i$ is the activation of nitric oxide synthase (NOS). This enzyme, which catalyzes the formation of NO from L-arginine, can be expressed in neurons (nNOS or NOS-1) as well as by activated microglia (iNOS or NOS-2). Increases in NO can react with cellular superoxide forming the damaging peroxynitrite and promote several forms of neurodegenerative diseases (Boje 2004). Tat affects both iNOS (Polazzi et al. 1999) and nNOS (Eugenin et al. 2007) by increasing $[Ca^{2+}]_i$ through release of intracellular stores (Krogh et al. 2014; Kruman et al. 1998) as well as through the Ca^{2+} influx obtained by activation of NMDA receptors (Haughey et al. 2001). The toxic effects of Tat-induced increases in $[Ca^{2+}]_i$ are mitigated by Ca^{2+} chelators as well as inhibitors of mitochondria Ca^{2+} uptake (Kruman et al. 1998), supporting the role of $[Ca^{2+}]_i$ dysregulation in Tat neurotoxicity.

In addition to plasma membrane Ca^{2+} channels, eukaryotic cells control Ca^{2+} homeostasis by Ca^{2+} channels located on endoplasmic reticulum (ER), mitochondria and other organelles, Ca^{2+} buffering proteins, and systems for Ca^{2+} extrusion and sequestration (Contreras et al. 2010). Thus, it is important to consider that Tat may also affect Ca^{2+} homeostasis in a NMDA receptor-

independent manner. Indeed, Tat has been shown to deplete both mitochondrial Ca^{2+} (Norman et al. 2007) and ER Ca^{2+} by activation of ryanodine receptors (Norman et al. 2008). Moreover, Tat appears to increase $[Ca^{2+}]_i$ by activation of L-type channels (Hu 2016). Our preliminary data presented in Fig. 3 support the view that Tat can also affect cytosolic Ca^{2+} in an NMDA-independent manner. In fact, MK801, a selective non-competitive NMDA receptor antagonist, failed to block Tat-mediated increase in $[Ca^{2+}]_i$ in cortical neurons in vitro (Fig. 3). This is in spite of the fact that the NMDA-mediated rise in $[Ca^{2+}]_i$ was prevented by the concurrent administration of MK801 (Fig. 3). Thus, it appears that Tat perturbs Ca^{2+} homeostasis by affecting both ER and other organelles controlling Ca^{2+} as well as Ca^{2+} regulating systems located in plasma membrane (Haughey et al. 2001). Irrespective of the ultimate mechanisms, all evidence points at altered Ca^{2+} homeostasis as one of the main mechanisms of Tat neurotoxicity (Haughey and Mattson 2002).

Gp120 appears to modulate $[Ca^{2+}]_i$ by a different mechanism. In fact, in contrast to Tat, gp120 increases $[Ca^{2+}]_i$ mostly by the mobilization of inositol triphosphate (IP_3)-sensitive calcium pools (Nath et al. 2000; Pandey and Bolsover 2000). This is supported by the data showing that inhibition of IP_3-sensitive but not ryanodine-sensitive ER calcium stores reduced gp120-evoked increases of Ca^{2+} (Hoke et al. 2009). Nevertheless, pathological consequences of a direct modification of ER Ca^{2+} stores are deleterious, exemplified by prominent dilation of the ER as well as enlarged mitochondria both in rodents and postmortem human brains (Norman et al. 2008).

As viral protein-induced mitochondrial toxicity has been repeatedly linked to disruption of Ca^{2+} homeostasis, it comes as no surprise that indirect ways to prevent Tat or gp120 toxicity include a blockade of receptor-mediated Ca^{2+} influx. This includes reduction of NMDA receptor activation by mild receptor antagonists, such as memantine, which has also been shown to protect neuronal function against gp120-mediated toxicity (Anderson et al. 2004; Nath et al. 2000).

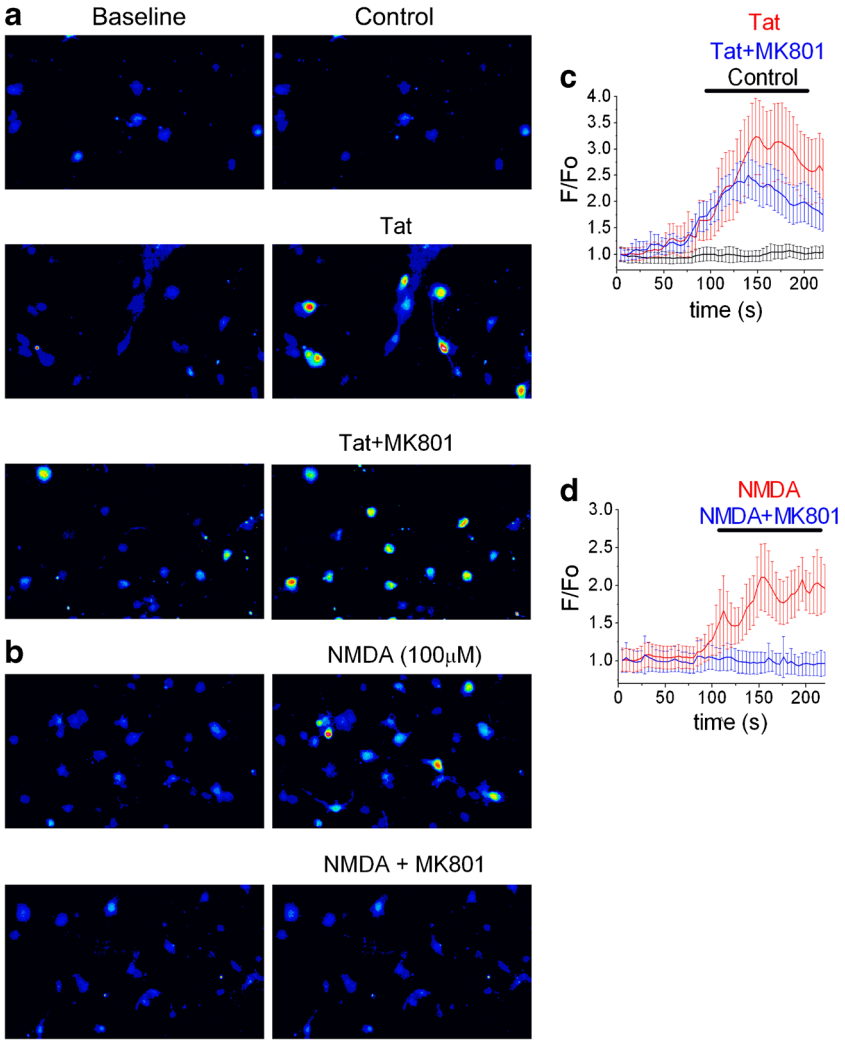

Fig. 3 Tat rapidly increases $[Ca^{2+}]_i$ in a NMDA receptor independent manner. Cultured rat cortical neurons (DIV7) prepared as described previously (Avdoshina et al. 2016b) were exposed for up to 200 s to recombinant Tat (100 nM) or NMDA (100 μM) alone or in combination with the NMDA receptor antagonist MK801 (60 μM). **a**, **b** Representative Fluo-4 fluorescence images of cortical neurons captured before (baseline) and after application of Tat or NMDA in the presence of absence of MK801. **c**, **d** Mean Fluo-4 fluorescence of **a** and **b**, respectively ($n > 20$ cells). Note that addition of Tat resulted in a significant increase in $[Ca^{2+}]_i$, which was not prevented when the NMDA receptor antagonist MK801 was added concurrently. Neurons were responsive to NMDA, which caused a rapid and robust rise in $[Ca^{2+}]_i$, prevented by the concurrent administration of MK801 **b** and **d**

Mitochondria Transport

Many recent investigations have identified disruption of mitochondrial dynamics and resulting neuronal dysregulation as mechanisms contributing to the toxicity observed in neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases (Mattson et al. 2008). Studies are beginning to identify mitochondrial abnormalities as causative factors for the neuropathology observed in HAND (Avdoshina et al. 2016a; Fields et al. 2016). The evidence for viral protein-induced mitochondrial impairment in neurons is plentiful, however many questions remain as to which mechanism(s) account for the abnormal mitochondria morphology/number in HAND.

Disruption of mitochondrial membrane potential, altered ATP production, and release of ROS can all be modulated through the dynamic processes of mitochondrial fusion and fission (Burte et al. 2015). Mitochondria are then transported to different cellular locations such as axons and dendrites, where ATP is in high demand. The proper intracellular distribution of mitochondria is essential for the maturation of dendritic spines (Li et al. 2004) and support of synaptic plasticity (Todorova and Blokland 2017). In addition, damaged and dysfunctional mitochondria are retrogradely transported to the some to be repaired.

Recently, Avdoshina et al. proposed a novel mechanism of HIV neurotoxicity that depends upon disrupted mitochondrial dynamics. The mechanism is based on the ability of gp120 to directly bind neuron-specific tubulin β-3 (Avdoshina et al. 2016b), a component of neuronal microtubules that plays a crucial role in anterograde and retrograde neuronal transport including mitochondria. The inhibition of this transport, as proposed for gp120, results in accumulation of damaged mitochondria in the synapses (Fig. 2) and elongated mitochondria in the soma (Avdoshina et al. 2016a). Thus, these mitochondria cannot deliver a continuous supply of ATP to axonal or dendritic terminals. Live imaging data of rodent neurons confirmed that gp120 elicits a profound impairment of mitochondrial trafficking to the point where mitochondria stop their bidirectional movement and alters fusion and fission (Avdoshina et al. 2016a). Defective mitochondrial transport has been suggested to cause synaptic injury in some neurodegenerative diseases (Burte et al. 2015; Itoh et al. 2013). Thus, impaired mitochondrial trafficking by gp120 could be one of the key pathogenic mechanisms to explain how HIV produces synaptic simplification and neuronal degeneration. Moreover, impaired trafficking in neurons can also contribute to depletion of neurotrophic support, and consequently reduce the number of synapses (Avdoshina et al. 2013).

The accumulation of impaired mitochondria can also have a significant impact on the health of neurons. Under normal circumstances, defective mitochondria will be disposed of through the mitochondria-specific process of mitophagy (Sheng 2014). Tat and gp120 may promote abnormal neuronal autophagy and degradation of critical intracellular components (Fields et al. 2015). Tat is known to increase the instance of association of Parkin-ring-like structures to the surface of injured mitochondria; however, it does not increase autophagic flux (De Simone et al. 2016). In another study with implications for mitophagy function, Tat induces disruption of the endolysosomal and autophagy pathways. These mechanisms are particularly important for mitochondrial health, since dysfunctional lysosomes could preclude homeostatic autophagy and mitophagy processes (Hui et al. 2012). As we know from investigations of other neurodegenerative diseases, these alterations in autophagy can be detrimental to neuronal function and survival. Further investigation into the direct impact of altered mitophagic flux will be important for understanding the implications in HAND.

Preventing HIV-Induced Mitochondrial Toxicity

No current therapy can target HIV proteins, allowing them to perpetuate their toxicity throughout the CNS. However, in vitro or in vivo investigations have identified potential therapeutic avenues that can mitigate the effects of viral protein-induced mitochondrial toxicity. Antioxidants, including Trolox, Cu/Zn SOD1, GPx1, and PACAP27 have been found in multiple in vitro experimental approaches to reduce Tat- and gp120- induced oxidative stress and prevent neuronal apoptosis (Agrawal et al. 2006; Agrawal et al. 2012; Butler et al. 2011; Pocernich et al. 2005; Rozzi et al. 2014). Ascorbate supplementation (ascorbate-2-O-phosphate) prevents the deleterious upregulation of iNOS and associated neuronal injury caused by gp120 in brain cell cultures (Walsh et al. 2004). Creatine is protective against Tat-induced ATP depletion, mitochondria membrane potential reduction, ROS production, and synapse loss (Stevens et al. 2014). Further, prevention of Tat endocytosis by heparan sulfate and dextran sulfate mitigated its mitochondrial neurotoxicity (Chauhan et al. 2003). Similarly, epicatechin, a flavonoid contained in food such as chocolate and green tea, has also been found to reduce Tat-mediated mitochondrial toxicity in cultured neurons (Nath et al. 2012), likely through the increase of the neurotrophin brain-derived neurotrophic factor (BDNF). This neurotrophin has a potent and widespread neuroprotective activity against several neurotoxins including gp120 (Bachis et al. 2003). Intriguingly, BDNF also prevents gp120-mediated neuronal apoptosis by decreasing the expression of the chemokine receptor CXCR4 (Bachis et al. 2003). In addition, BDNF has been known to induce mitochondrial biogenesis in newly generated neurons (Cheng et al. 2012), and to stimulate brain mitochondrial metabolism by increasing the efficiency of respiratory coupling and ATP synthesis (Marosi and Mattson 2014). Recently, BDNF has been shown

to regulate mitochondrial transport and distribution in neurons promoting the docking of the organelles at sites of synaptic transmission, thereby facilitating neurotransmission (Su et al. 2014). Thus, it is plausible that BDNF is neuroprotective against HIV because it restores the proper mitochondrial function that is impaired by Tat and gp120.

Adding to the complexity of Ca^{2+} influx in Tat or gp120-mediated neurodegeneration is the fact that both these viral proteins can kill neurons by a non-cell-autonomous mechanism. For example, the neurotrophin receptor p75NTR, a member of tumor necrosis factor of receptors, has been show to promote apoptosis (Bredesen and Rabizadeh 1997) and axonal degeneration (Singh et al. 2008). This receptor induces long-term depression through Ca^{2+} influx (Woo et al. 2005). Gp120 indirectly activates p75NTR by increasing the levels of the BDNF precursor protein, proBDNF (Bachis et al. 2012), which, in turn, causes loss of dendritic spines (Bachis et al. 2016) and negatively influences other forms of synaptic plasticity (Yang et al. 2014). Small molecules like LM11A-31, which inhibit p75NTR (Pehar et al. 2006), or blocking antibodies against p75NTR (Bachis et al. 2012) are able to protect neurons from HIV-induced toxicity either by blocking calcium accumulation (Williams et al. 2016) or reducing p75NTR-mediated activation of pro-apoptotic signal (Bachis et al. 2012). A clear challenge in the field is to validate the data obtained in animal models to HAND subjects. Nevertheless, animal and human studies of HAND samples have confirmed that proBDNF levels are up-regulated and are a primary cause of neuronal loss (Bachis et al. 2012).

Conclusion

Due to the efficacy of antiretroviral therapies, the population of HIV-infected individuals continues to age (Saylor et al. 2016). In 2013, people aged 55 and older accounted for more than one quarter of the estimated 1.2 million people living with diagnosed or undiagnosed HIV in the USA. While this expanded lifespan is wholly a good thing for the patient population, it comes with an added layer of complexity in terms of the neurocognitive impairments observed in the same population. Some aging paradigms feature mitochondria and numerous studies find mitochondrial changes occur with normal aging (Balaban et al. 2005; Gadaleta et al. 1998; Mattson et al. 2008). Combined with the neurotoxic effects of HIV proteins such as Tat and gp120, the neurocognitive impairments observed in these patients are likely to increase in incidence and severity. Continued exploration of the combined effects of aging and HIV proteins will be important to uncover mechanisms at play and to develop therapies to combat such neuronal disruptions.

Decades of research have identified numerous mechanisms of toxicity by which HIV, through viral proteins, impairs neuronal function and health, contributing the cognitive impairments observed in HAND. Nevertheless, therapies specifically targeting the neuronal degeneration seen in HAND are still unavailable, mostly due to an incomplete understanding of all mechanisms used by viral proteins to promote neurodegeneration. The viral protein-induced mitochondrial impairment is one crucial aspect of HIV neurotoxicity. Further investigation into the direct effects of Tat and gp120 upon mitochondria and their dynamic processes will strengthen the field and likely enable the development of beneficial treatments for those with HAND in the future.

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