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HIV-associated neurodegeneration: exploitation of the neuronal cytoskeleton

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Abstract

Human immunodeficiency virus-1 (HIV) infection of the central nervous system damages synapses and promotes axonal injury, ultimately resulting in HIV-associated neurocognitive disorders (HAND). The mechanisms through which HIV causes damage to neurons are still under investigation. The cytoskeleton and associated proteins are fundamental for axonal and dendritic integrity. In this article, we review evidence that HIV proteins, such as the envelope protein gp120 and Transactivator of transcription (Tat), impair the structure and function of the neuronal cytoskeleton. Investigation into the effects of viral proteins on the neuronal cytoskeleton may provide a better understanding of HIV neurotoxicity and suggest new avenues for additional therapies.

Keywords

BDNF; gp120; neurodegeneration; actin; Tat; microtubules

Introduction

Human immunodeficiency virus (HIV), which depletes the cells of the immune system, also infects the central nervous system (CNS) and promotes direct neurotoxic pathology and neurocognitive impairments termed HIV-associated neurocognitive disorders (HAND). Symptoms of HAND can range in severity from asymptomatic neurocognitive impairment (ANI), to minor neurocognitive disorder (MND) and HIV-associated dementia (HAD) (Tan and McArthur, 2011). The HIV-positive population continues to age as combined antiretroviral therapy (cART) successfully reduces HIV-mediated immune dysfunction (Sandler and Sereti, 2014; Crowell et al., 2016). However, even with suppression of viral load in the periphery, this population still demonstrates cognitive impairments and memory loss (Tozzi et al., 2007; Heaton et al., 2010; Gates et al., 2016). Within this aging population (Mahy et al., 2014), the prevalence of cognitive alterations is increasing and over 50% of

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HIV-positive patients will develop neurocognitive symptoms (Sacktor et al., 2002; Clifford and Ances, 2013). HIV-positive individuals are seven-times more likely to experience a mild cognitive impairment than their age-matched HIV-negative counterparts, even when adhering to cART and having undetectable viral load in the periphery (Sheppard et al., 2015). In addition, there is evidence that the CNS serves as a reservoir for HIV replication (Fois and Brew, 2015), thereby limiting the prospect of complete viral eradication.

Before cART, the pathology of HAND included robust neuronal apoptosis, with multinucleated giant cells and astrogliosis in cortical and subcortical areas (Adle-Biassette et al., 1995; Petito and Roberts, 1995; Kaul et al., 2001). Clinically, these patients exhibited motor and cognitive impairments (Price et al., 1988; Heaton et al., 2011). However, with the introduction of cART, HAND pathology has shifted considerably. In fact, there is a reduction in widespread brain atrophy, which was commonly observed in the pre-cART era (Gongvatana et al., 2009). Notably, these patients lack robust neuronal cell loss but the gray matter of cART-treated HIV subjects contain neurons with damaged synapses and axons, as well as short dendrites, a neuropathological condition referred to as synaptic simplification, or “synaptopathy” (Masliah et al., 1997; Ellis et al., 2007). This neuropathological presentation may be reflected by the decrease in prevalence of the most severe category of HAND, HAD, which has declined from about 15–20% to 2–8% of the HIV-positive population, and increases in the two less-severe categories, MND and ANI, from 25–30% to 50–60% (Heaton et al., 2010; Saylor et al., 2016). Nevertheless, HAND subjects still exhibit thinning of several regions including the cerebral cortex (Nichols et al., 2018) as well as the subcortical regions of hippocampus and basal ganglia (McArthur, 2004; Alakkas et al., 2018).

The underlying causes of synaptic simplification observed in these subjects remain under investigation. These pathological features can be seen in the HAND population, even though HIV cannot productively infect neurons (Kanmogne et al., 2000). One of many challenges facing the neuroAIDS field is the integration of mechanisms of neuronal loss due to secondary or indirect effects, such as inflammation, with those pertaining to the direct neurotoxicity of viral proteins. A further understanding of the core pathophysiological mechanisms for HAND will eventually assist in the development of additional therapies. It is important to note that HIV encephalitis (HIVE), a neuro-inflammatory condition characterized by the presence of HIV infected microglial cells, microglial nodules, multinucleated giant cells, astrogliosis and myelin loss (Wiley and Achim, 1994; Anderson et al., 2002; Everall et al., 2005), does not entirely explain the mechanism of synapto-dendritic loss. Indeed, current cART, which prolongs the life span of HIV-positive subjects, may reduce HIVE but does not prevent the activation of microglia (Ginsberg et al., 2018; Rubin et al., 2018) or HAND (Gelman, 2015). Therefore, many recent studies have focused on the neurotoxic effects coordinated by HIV proteins, and their molecular and cellular mechanisms that lead to direct neuronal loss (Kanmogne et al., 2002; Nath, 2002). As the basic mechanisms activated by HIV proteins become better understood, novel strategies can be devised to prevent their neurotoxicity.

In this review, we summarize evidence indicating a mechanism of direct neurotoxicity by HIV proteins via alterations in the neuronal cytoskeleton structure and function. Because the

cytoskeleton is important for determining the mechanical properties of synapses, impairments in the cytoskeleton can easily explain the synaptopathy seen in HAND. Thus, in addition to therapeutics aimed at reducing viral load, alternative drug therapies that reduce synaptopathy should be developed and applied.

Neuronal cytoskeleton and neurodegenerative diseases

The ability of neurons to receive and transmit signals and impulses depends on their polarized organization. The neuronal cytoskeleton is crucial for the establishment and maintenance of spatial organization and architectural support of axons and dendrites. In addition, the cytoskeleton is crucial to preserve the functionality of intracellular transport and dendritic spines. The neuronal cytoskeleton is made of microtubules, actin, neurofilaments, and their associated proteins.

Microtubules

Microtubules (MTs) are dynamic structures consisting of α- and β-tubulin heterodimers (Nogales et al., 1998), that have several functions within a cell, including formation of mitotic spindles for cell division. In neurons, MTs are found both in axons and dendrites and are primarily responsible for long-distance intracellular transport of cargo. As post-mitotic cells, neurons require localized, targeted movement of cargo between the cell soma and distal dendritic and axonal segments. MTs are intracellular highways and are assembled in a head-to-tail manner to form highly polarized filaments upon which cargo is directed in a controlled fashion. Impairments in the highly-regulated and dynamic process of MT growth and shrinkage inhibit the trafficking of essential organelles, including mitochondria and cargo-containing vesicles (Cartelli et al., 2010). Impairments in neuronal MTs and therefore the trafficking of cargo are detrimental to neuronal health (McMurray, 2000; Cartelli et al., 2010; Baird and Bennett, 2013). For example, neurons with inefficient MT-based transport of neurotrophic factors, which are essential for preserving the integrity of neurons, causes degeneration of dendrites and axons (Mariga et al., 2017). Thus, interruption of MT-based transport has been suggested to play a role in the development of neurodegenerative diseases including Huntington's (HD) and Alzheimer's diseases (AD) (Millecamps and Julien, 2013). As HIV-positive subjects age, there is much to learn by examining the mechanisms discovered for other diseases of aging to fully characterize similarities and differences between HAND and other neurodegenerative diseases.

Stability of MT

MTs are dynamic structures and undergo cycles of tubulin polymerization and depolymerization, which alter their functionality and length. This directed, dynamic instability is crucial for MT function and is regulated by interactions with other intracellular factors. These include MT-associated motor proteins of the kinesin (Verhey and Hammond, 2009) and dynein (Vallee et al., 2004) families, as well as non-motor MT associated proteins (MAPs), such as tau and MAP2.

The assembly of tubulin dimers into fully functional MTs and the properties of these formed MTs are also modified by post-translational modifications (PTMs) such as phosphorylation,

acetylation, tyrosination, and others (Westermann and Weber, 2003). For instance, acetylation occurs after MT assembly, promotes stabilization, and consequently neuronal survival. Acetylation of tubulin is enriched in the axon when compared to dendrites (Fig. 1) and contributes to the successful transport of cargo along axons (Cambray-Deakin and Burgoyne, 1987). In fact, deacetylation of tubulin following activation of histone deacetylase (HDAC)-6 (Hubbert et al., 2002) reduces axonal regeneration and inhibition of this enzyme protects neurons after injury (Rivieccio et al., 2009). Tubulin detyrosination affects MT interactions with intermediate filaments, another component of the cytoskeleton. In addition, tyrosination, polyglutamination, and other PTMs affect the binding of motor and non-motor proteins to MTs (Song and Brady, 2015). Thus, PTMs on fully formed MTs modify many aspects of neuronal function.

Non-motor proteins known to regulate MT stability and influence molecular motor transport include tau (Hirokawa et al., 1988), MAP2 (Lewis et al., 1988), and MAP4 (Olson et al., 1995). Within the CNS, tau and MAP2 are exclusively found in neurons (Dehmelt and Halpain, 2005). Tau, the main constituent of the neurofibrillary tangles observed in AD, is present mainly in axons, whereas MAP2 segregates in dendrites and cell bodies (Dehmelt and Halpain, 2005). Tau stabilizes axonal MTs (Binder et al., 1985) and, when phosphorylated, inhibits kinesin-1 motility (Dixit et al., 2008; Stern et al., 2017) most likely by disrupting MTs (Drewes et al., 1997). MAP2 binding to tubulin also favors stability of MTs, however, MAP2 phosphorylation may also impair MAP2 function and consequently, its ability to stabilize MTs (Sanchez et al., 2000). The emerging picture is indicates a complex, tightly-regulated process of MT dynamics that, when pathologically targeted, promotes neurodegeneration.

Actin

Actin is a highly conserved and abundant cytoskeleton protein that in neurons plays a role in axonal elongation, the formation and maintenance of growth cones, presynaptic terminals, dendritic spines, and synaptic homeostasis (Coles and Bradke, 2015). Actin exists as soluble monomers (G-actin) as well as actin filaments (F-actin). F-actin, together with MTs, is a key mediator of neuronal polarity and formation of dendritic structures (Pacheco and Gallo, 2016). F-actin is also an important component of dendritic spines, essential protrusions along dendrites that harbor synapses. In addition, F-actin forms patches, longitudinal fibers that traverse the lengths of dendrites (D'Este et al., 2015), and rings (Konietzny et al., 2017). The dynamics of F-actin, including stability and expression levels, is enhanced by long-term potentiation and impaired by long-term depression (Fukazawa et al., 2003; Szabo et al., 2016). Overall, actin plays a role in support of neurite shape, stabilization of the cytoskeleton (Qu et al., 2017), and synaptic plasticity (Bar et al., 2016). Because of these roles, accumulation of actin or alterations to the actin cytoskeleton have been shown to induce neurotoxicity that results in various neurological diseases such as Parkinson's disease (PD) (Ordonez et al., 2018) and AD (Fulga et al., 2007; Bamburg et al., 2010).

Neurofilaments

Neurofilaments (NFs) are intermediate filament cytoskeleton proteins that interact with MTs in axons, provide structural support, maintain axon caliber, and affect the transmission of

electrical impulses along axons (Yuan et al., 2012). NFs consist of several components that differ in molecular size: light (70–86kDa), medium/intermediate (145–160kDa) and heavy (200–220kDa) chains, as well as α-internexin (58–66kDa) (Liem and Messing, 2009; Khalil et al., 2018). Because of their abundance and the exclusive expression of NFs in neurons, cerebrospinal fluid (CSF) or blood serum levels of NF-light chain (NF-L) has been used as a biomarker to detect axonal damage/degeneration in acute and chronic neurological disorders (Khalil et al., 2018).

In HAND subjects, levels of NF-L have been used to predict neuronal injury. In fact, high levels of NF-L are found in both plasma and CSF plasma when compared to healthy controls. Importantly, NF-L levels correlate with higher viral loads (Gisslen et al., 2016) and neurocognitive impairments, and are reduced in subjects under cART (Jessen Krut et al., 2014). In addition, elevated NF-L levels in the CNS has been found in some patients up to two years before onset of HAD (Gisslen et al., 2007), suggesting that HIV promotes axonal injury even in the mildest form of HAND.

This loss of NF-L in neurons can be recapitulated *in vitro*. Prolonged (21 days) exposure of “neurospheres” derived from human neuroepithelial progenitor cells to either HIV or its envelope protein, gp120, reduces the expression of neuron-specific NF-L, without altering the expression of astrocytic intermediate filament protein, glial fibrillary acidic protein (GFAP) (McCarthy et al., 2006). Based on the specific roles of NFs in axons, the loss of NFs could explain the pathology of axonal degeneration seen in HAND subjects. However, whether the loss of NFs is a consequence or the cause of neurodegeneration observed in HAND subjects is not well established.

HIV proteins and Neurodegeneration

HIV proteins and neuronal MTs

In immune cells, the host cell’s cytoskeleton is crucial for the HIV life cycle. The virus uses its proteins and a variety of strategies to manipulate the cytoskeleton to enhance entry and stabilize the transport of genetic material to the cell nucleus. Manipulation of host cell’s cytoskeleton improves replication and infection, and ultimately the release of new viral particles (Ospina Stella and Turville, 2018). Contrastingly, in the CNS, HIV cannot infect neurons and instead utilizes its viral proteins to destabilize and damage neurons. Soluble viral proteins that induce neurodegeneration include the transactivator of transcription, Tat, and the envelope protein gp120. These proteins are produced in the brain of HIV-positive individuals (Keys et al., 1993; Di Stefano et al., 1996; Bachani et al., 2013; Johnson and Nath, 2016) and are released in the extracellular space from HIV-infected cells. Both proteins undergo uptake by neurons and can travel along axons to cause injury at distal regions (Bruce-Keller et al., 2003; Bachis et al., 2006). The degeneration caused by these proteins in animal models is similar to that observed in HAND. For instance, both Tat and gp120 have been shown to be neurotoxic to various neuronal populations *in vivo* (Sabatier et al., 1991; Bansal et al., 2000; Maragos et al., 2003; Acquas et al., 2004). Transgenic mice in which Tat can be inducibly expressed under the GFAP promoter show evidence of learning and memory deficits (Carey et al., 2012), associated thinning of the cortex (Carey et al., 2013), and synaptodendritic injury (Fitting et al., 2013). Likewise, transgenic mice

expressing the envelope protein gp120 under the GFAP promoter exhibit neuronal loss and dendritic simplification (Toggas et al., 1994), altered long-term potentiation in the hippocampus (Krucker et al., 1998), reduced neurogenesis (Lee et al., 2013), and loss of dendritic spines in the hippocampus (Bachis et al., 2016). Importantly, the neurotoxic effects of viral proteins in animal models are also seen in HAND and the pathological features demonstrate good correlation with the severity of neurocognitive decline. These features include synaptodendritic injury (Masliah et al., 1992), mitochondrial damage (Haughey and Mattson, 2002; Langford et al., 2004; Fields et al., 2016) and loss of neurotrophic factors (Bachis et al., 2012). Thus, Tat and gp120 animals have gained increased attention as experimental models to study mechanisms of neurotoxicity and possible treatment targets.

More recently, a new line of investigation has proposed that Tat and gp120 are neurotoxic after their endocytosis into neurons. Tat enters neurons in a receptor-independent manner (Liu et al., 2000) and can bind to MTs to induce neuronal damage (Chen et al., 2002; Aprea et al., 2006) as demonstrated by the decreased expression and altered distribution of in MAP2 positive processes (Langford et al., 2018). Unlike Tat, gp120 is internalized by neurons primarily in a chemokine receptor/clathrin-dependent manner (Wenzel et al., 2017). Once endocytosed, gp120 is axonally transported both *in vitro* and *in vivo* (Bachis et al., 2006; Melli et al., 2006; Ahmed et al., 2009; Berth et al., 2015) to adjacent neurons. The axonal transport process requires gp120 to bind to MTs by forming a vesicular complex with mannose binding lectin (Teodorof et al., 2014), a carrier that facilitates glycoprotein trafficking (Nonaka et al., 2007). Alternatively, once inside neurons, gp120 can bind to the neuronal specific beta III tubulin (Avdoshina et al., 2016a). Intriguingly, this binding occurs through a conserved helix domain rather than the hypervariable region 3 (V3) of gp120, which is responsible for the phenotypic diversity of HIV. The direct interaction of Tat or gp120 with MTs impairs the formation/polymerization of MTs (Butler et al., 2011) and gp120 decreases the acetylation of tubulin (Avdoshina et al., 2017). Deacetylated MTs have a lower affinity for the motor proteins of kinesin-1 and dynein (Reed et al., 2006); thus, gp120 or Tat may impair MT-based, axonal transport by altering MAPs.

Viral proteins exhibit a direct effect on MTs, nevertheless, we cannot exclude that some of the neurotoxic effects of these proteins encompass other mechanisms. For instance, gp120 could also alter the neuronal cytoskeleton through signaling of chemokine co-receptors CXCR4 or CCR5. These receptors, which are expressed by several neuronal populations *in vivo* (Klein et al., 1999; Stumm et al., 2003; Maung et al., 2014), promote phosphorylation and inactivation of glycogen synthase kinase-3 beta (GSK3β) (Chalasani et al., 2003), a signaling molecule involved with MT assembly in axons (Zhou and Snider, 2005). Although controversy exists whether inactivation of GSK3β is beneficial or detrimental to neurons, it certainly alters MT dynamics and stability (Conde and Caceres, 2009). Thus, chemokine co-receptor signaling may also contribute to alterations of the neuronal cytoskeleton caused by viral proteins.

MT stability and axonal transport

There are several cellular events that could explain how binding of gp120 and Tat to MTs induces neurodegeneration. These include impaired axonal transport through altered MT

stability, changes in neuronal morphology, and possibly decreased expression of NFs and axonal diameter (Hoffman et al., 1987).

One of the immediate consequences of viral protein impairment of MT structure and function may be the decreased axonal transport of mitochondria. These essential organelles are highly dynamic and control high-energy intermediates, including adenosine triphosphate (ATP). Neuronal function depends on ATP because these cells have a high energy demand and require ATP at distal areas including axonal and dendritic synapses (Dickey and Strack, 2011; Merrill et al., 2011; Berthet et al., 2014). Moreover, mitochondria play a role in spine maturation and neuronal survival. They regulate Ca^{2+} homeostasis, thus affecting neurotransmission and synaptic plasticity (Levy et al., 2003), as well as reduce the production of reactive oxygen species, which is crucial for neuronal survival (Gleichmann and Mattson, 2011). In order to maintain energy homeostasis and to continue essential activities, neurons must precisely establish an adequate distribution of mitochondria to axons and dendrites through the process of fusion and fission (Westermann, 2010; van der Bliek et al., 2013). Fusion is the process of exchanging mitochondrial DNA and other components, with the goal of repairing damaged mitochondria. The opposite process, fission, is required for mitochondrial transport. Both processes utilize various proteins such as mitofusins, and GTPase dynamin-related protein (DRP), located on the outer membrane of mitochondria, and optic atrophy protein 1, located in the inner membrane.

Mitochondrial fission and distribution are impaired in HAND brains (Fields et al., 2016). Further, the distribution and function of mitochondria is altered in many animal models of HAND including gp120 transgenic mice (Avdoshina et al., 2016b), Tat transgenic mice (Rozzi et al., 2018), and HIV transgenic rats (Villeneuve et al., 2016), which express gp120 and Tat as well as five other viral proteins. Gp120 brings mitochondrial movement to a halt (Avdoshina et al., 2016b) whereas Tat causes an accumulation of mitochondria at the cell soma (Rozzi et al., 2018). This suggests that HIV, though its viral proteins, alters the axonal transport of mitochondria. Further, those mitochondria that accumulate defective proteins or DNA must be either repaired by fusion with healthy mitochondria or cleared from the cell by selective process of mitophagy (Twig et al., 2008). For this processes, axonal transport is essential because mitochondria need to be retrogradely transported to the cell body by MTs to be repaired or degraded. Both gp120 and Tat impair mitophagy, creating an accumulation of damaged mitochondria in the cell (Teodorof-Diedrich and Spector, 2018). Furthermore, altered transport could interfere with the natural process of autophagy, which clears misfolded or foreign proteins from the cytoplasm. In neurons, autophagy is slightly different from that in other cells because autophagosomes are formed at the neurite tip and undergo dynein-mediated retrograde transport to their site of functionality, the soma (Maday et al., 2012). When this maturation is prevented, autophagy is impaired. This could be the mechanism through which HIV proteins Vpr (Dumas et al., 2015), Tat (Fields et al., 2015), and Nef (Kyei et al., 2009), interfere with autophagy and initiate neurodegeneration.

There are additional functional implications of impaired MT function that could explain how HIV proteins damage neurons. One is the loss of anterograde transport of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), and synaptic vesicle containing neurotransmitters. Neurons use these biomolecules at the presynaptic site to maintain

synaptic function and plasticity. Likewise, neurotransmitter receptors earmarked for degradation or other biomolecules involved in retrograde signaling must be returned to the cell body by retrograde transport. Anterograde and retrograde transport involves kinesin-1 and dynein (Bhattacharyya et al., 2002; Chowdary et al., 2015; Sainath and Gallo, 2015). Thus, an effect on motor proteins could decrease neurotrophic support and change levels of neurotransmitters and their receptors. These alterations, which are suggested mechanisms for the atrophy of neurons in neurodegenerative diseases including HD and Amyotrophic lateral sclerosis (ALS) (Hirokawa et al., 2010; Hinckelmann et al., 2013; Millecamps and Julien, 2013), are now considered also to explain reduction in synaptic connectivity in HAND (Kumar et al., 2011; Fields et al., 2014; Mocchetti et al., 2014; Zhu et al., 2018). Nevertheless, neuronal atrophy induced by impaired BDNF axonal transport can be significantly limited by restoring BDNF transport (Zhao et al., 2016). Likewise, therapeutic compounds that increase neurotransmitter levels are neuroprotective against HIV-mediated neuronal injury (Schifitto et al., 2009; Steiner et al., 2015). Thus, drugs that can restore axonal transport of neurotrophic factors, cargo containing vesicles, and mitochondria have potential therapeutic significance for HAND.

Lastly, impairment in axonal transport, which is a direct mechanism of neurotoxicity by viral proteins, may be compounded with a pro-inflammatory environment. For instance, interleukin-1 β (IL-1β), a pro-inflammatory cytokine that is released from microglia or infiltrating monocytes in response to gp120 or Tat (Koka et al., 1995; Yang et al., 2010), decreases the retrograde transport of BDNF (Carlos et al., 2017). Additionally, after exposure to gp120 or Tat, astrocytes release reactive oxygen species. Impairment in axonal transport of mitochondria occurs quickly after exposure to exogenous H_2O_2, a mimetic for a redox-rich environment (Errea et al., 2015). Therefore the direct effects of viral proteins and a pro-inflammatory or redox-rich environment may be additive in impairing MT-based, axonal transport.

Viral proteins and dendritic spines

Investigation into how viral proteins regulate synapse loss through the cytoskeleton is crucial for the development of therapeutics to prevent this degeneration. In neurons, actin plays a large role in the formation of dendritic spines (Matus, 2000; Hotulainen and Hoogenraad, 2010). Dendritic spines are considered important postsynaptic contact sites for learning and memory. Consistent with this notion, suppression of actin dynamics inhibit long-term potentiation (LTP) (Krucker et al., 2000), which forms the basis for learning and memory. Dendritic spines are damaged and synaptic density is decreased in humans with HAND (Ellis et al., 2007) and in neurons exposed to gp120 or Tat *in vitro* (Viviani et al., 2006; Shin et al., 2012; Bertrand et al., 2014) or *in vivo* (Bachis et al., 2016; Raybuck et al., 2017). The decrease in dendritic spine density is a predictor of cognitive deficit (Yang et al., 2009). Complementary to these data, several investigators have established that Tat prevents LTP when injected intracerebroventricularly (icv) in mice (Li et al., 2004) or when applied to hippocampal slices (Behnisch et al., 2004). Similarly, HIV-derived gp120 impairs LTP both *ex vivo* (Dong and Xiong, 2006) and in rodents, including gp120 transgenic mice (Krucker et al., 1998) and rats injected icv with gp120 (Sanchez-Alavez et al., 2000). Although more studies are needed to reach a definitive conclusion about the mechanism whereby HIV

reduces dendritic spines, a direct effect of viral proteins on the cytoskeleton dynamics could explain cognitive deficits seen in HAND.

Studies investigating other neurodegenerative diseases allow us to speculate on mechanisms that cause the alterations in dendritic spines in HAND. First, dysregulation of Rho-GTPase family signaling alters actin dynamics. This is seen in different brain areas of subjects with PD, HD, and AD (Eira et al., 2016). In T-cells, HIV, through its envelope protein binding to CD4 and chemokine co-receptors, activate Rho GTPases (Lucera et al., 2017); however, investigation into the effect of HIV proteins on this signaling in neurons is still in early stages. One of the canonical members of the Rho GTPase family that is activated by Tat is RhoA (Krogh et al., 2015). RhoA recruits its specific kinase (ROCK), which modulates MT dynamics and cell polarity, and remodeling of the actin cytoskeleton (Sit and Manser, 2011), leading to N-methyl-D-aspartate (NMDA) receptor dysfunction among other problems (Krogh et al., 2015). A defective NMDA receptor is particularly important in the context of HAND because Tat has been shown to induce neuronal apoptosis by binding to NMDA receptor and affecting its function (Haughey et al., 2001; Eugenin et al., 2007; Li et al., 2008). Activation of the NMDA receptor can change the dynamics of the cytoskeleton because it decreases the phosphorylation of MAP2 (Quinlan and Halpain, 1996). Phosphorylation of MAP2 is crucial for its association with MTs and their stability. Thus, the modulation of the phosphorylated state of MAP2 by NMDA-glutamate receptors may be implicated in dendritic plasticity. Furthermore, NMDA treatment induces ICAM-5 dependent alpha-actinin clustering (Tian et al., 2007), a cellular mechanism that could also affect the integrity of the actin cytoskeleton. Thus, Tat activation of NMDA might alter the properties of MAPs that could account for some of the negative effects of glutamate on postsynaptic neurons.

Additionally, this signaling cascade regulates actin-binding proteins (ABP), whose functions in the cytoplasm include actin cytoskeletal organization in repose to intracellular and extracellular stimuli (Rajakyla and Vartiainen, 2014). One key ABP is cofilin which coordinates the spatial organization of actin filament assembly/disassembly (Bamburg and Bernstein, 2010). When activity or the PTMs of cofilin is impaired, actin-based transport is inhibited resulting in protein aggregation and neuronal loss (Minamide et al., 2000). Although not yet examined in neurons, the activation of chemokine receptor signaling in HIV infected T-cells causes dephosphorylation of cofilin and decreased expression of F-actin (Cameron et al., 2010). Therefore, either chemokine receptor-mediated or Rho GTPase-mediated signaling may be a mechanism through which gp120 and Tat damage dendritic spines.

Conclusions

Intact cytoskeleton organization, efficient intracellular transport, and functional dendritic spines are key for neuronal health and survival. However, investigation into how HIV and HIV proteins impair the neuronal cytoskeleton should be further explored. There are several existing mechanisms through which HIV proteins may alter the neuronal cytoskeleton. First, direct binding of HIV proteins, including gp120 (Avdoshina et al., 2016a) and Tat (Chen et al., 2002; Aprea et al., 2006), could modify MT dynamics and stability. Further, gp120 binds

to the terminal tail of beta III tubulin (Avdoshina et al., 2016a), which contains the binding site for kinesin-1 through three essential amino acids E410, D417, and E421 (Uchimura et al., 2006). Consequently, gp120 may prevent the recruitment of MAPs, including motor proteins, to MTs. Moreover, gp120 and Tat binding to MTs could reduce the anterograde transport of neurotrophic factors and therefore diminish their activity-dependent release, which ultimately, could impair the survival of postsynaptic neurons. Both Tat and gp120 impair neuronal MT polymerization (Butler et al., 2011; Avdoshina et al., 2017), which may be an additional mechanism whereby HIV proteins interfere with MT dynamics. MT impairment has detrimental consequences for many intracellular processes including transport of mitochondria, cargo-containing vesicles, neurotrophic factors, and autophagy/mitophagy, among others.

In addition to tubulin, neuronal health and functionality is regulated by actin. During development, the actin cytoskeleton supports the formation, extension and branching of neurites and dendritic spines. In the adult CNS, spines containing excitatory synapses need to be strengthened to support learning and memory. Viral proteins gp120 and Tat both cause decreased spines in animal models of HAND (Bachis et al., 2016; Raybuck et al., 2017) and primary neurons *in vitro* (Shin et al., 2012; Bertrand et al., 2014). The functionality of dendritic spines is also impaired with viral proteins. These alterations may occur due to signaling through Rho GTPases or chemokine receptors. However, signaling is not the only potential mechanism through which HIV proteins alter actin and actin dynamics. Similar to MTs, F-actin and its regulatory protein, cofilin, can undergo PTMs which regulates their functionality will cause dysregulation of the actin cytoskeleton (Terman and Kashina, 2013). NMDA receptor activation, a well-characterized mechanism of Tat toxicity (Haughey et al., 2001; Song et al., 2003) causes phosphorylation of cofilin and dephosphorylation of MAP2 (Quinlan and Halpain, 1996). Intriguinly, NMDA-mediated dephosphorylation of MAP2 occurs through the calcium/calmodulin-dependent protein phosphatase calcineurin (Quinlan and Halpain, 1996), which is also activated by Tat *in vitro* (Rozzi et al., 2018) or in infected patients (Hu, 2016), suggesting a commonality of signaling mechanism between Tat and NMDA in altering the cytoskeleton dynamic.

In conclusion, cytoskeletal proteins could play a role in long-term synaptic modifications occurring in infected patients. Binding to actin, tubulin, and intermediate filaments by the viral proteins gp120 and Tat could lead to altered function of these specialized cells and ultimately a decrease in their survival (Fig. 2). The impact of these viral proteins, as well as several other HIV proteins including Nef and Vpr, on the neuronal cytoskeleton is a new mechanism to explain the synaptopathy seen in HAND. The mechanisms though which these alterations occur- direct binding, signaling, or altered network dynamics- still need to be fully uncovered. Current and future studies will inform whether the neuronal cytoskeleton should be targeted therapeutically to mediate the cognitive deficits seen in HAND.

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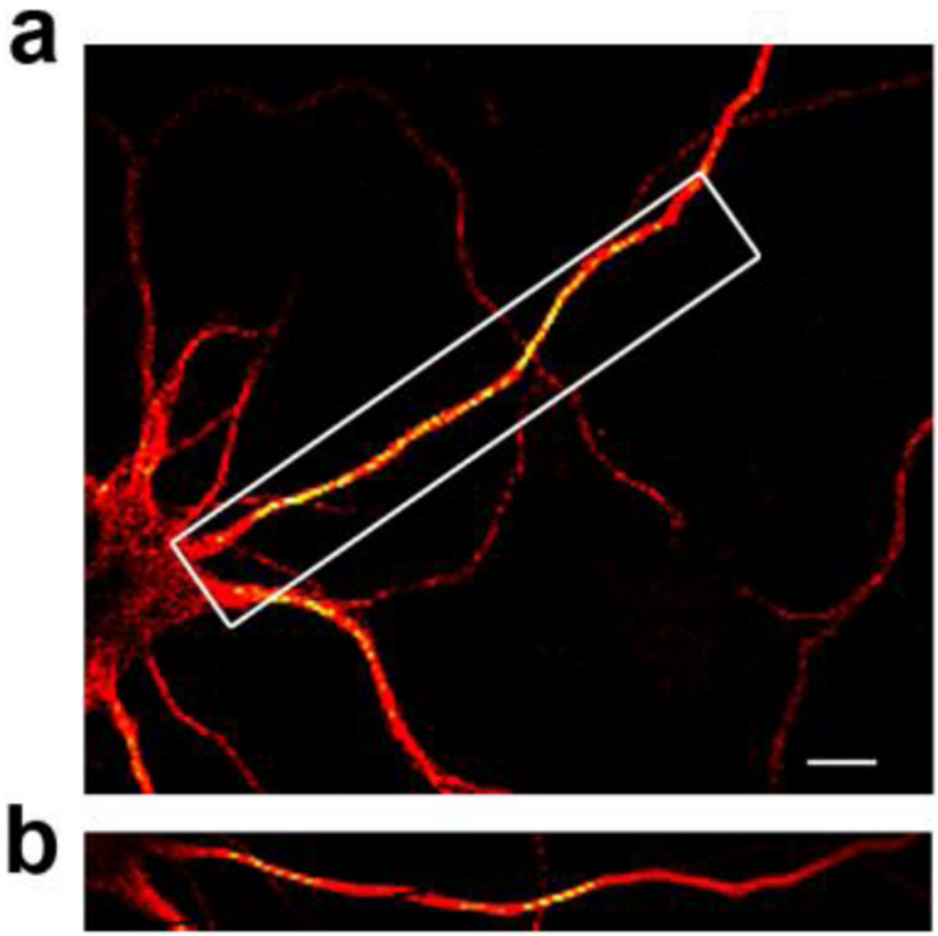

Figure 1. Acetylated tubulin is enriched in the axon.

a) Primary rat cortical neurons (7 days *in vitro*) were fixed, stained for acetylated tubulin (red), and imaged using a STEDYCON microscope (Abberior Instruments). Yellow, a coloring construct from the imaging system, indicates the enrichment of acetylated tubulin. b) Enlarged image of box in (a) showing that acetylated tubulin is enriched in the axon when compared to the rest of the cell. Scale bar: 5nm.

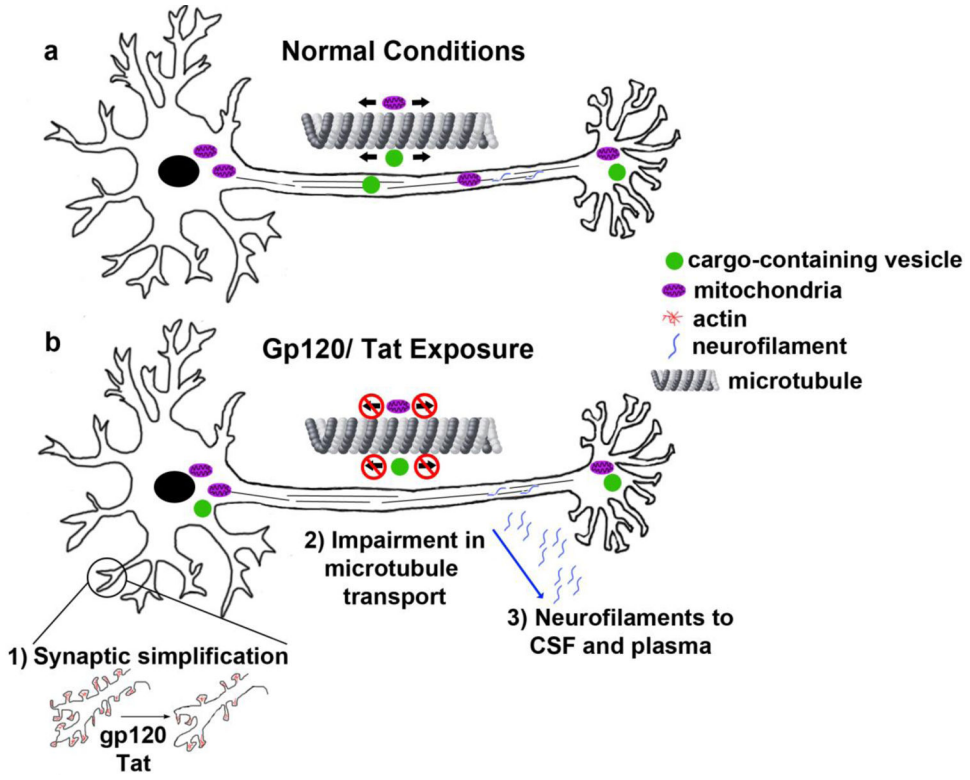

Figure 2. Schematic of the effect of HIV proteins on the neuronal cytoskeleton.

a) Under normal conditions, neurons are able to transport mitochondria and cargo-containing vesicles bidirectionally (arrows) along microtubules. b) Viral proteins gp120 and Tat cause several impairments to the neuronal cytoskeleton including: 1) Synaptic simplification due to alterations in actin and actin binding proteins; 2) Impairment in microtubule based transport including decreased motility of mitochondria and cargo-containing vesicles; 3) Loss of proper localization of neurofilaments and increased levels in the cerebral spinal fluid (CSF) and blood plasma.