



Cal‘MAM’ity at the Endoplasmic Reticulum-Mitochondrial Interface: A Potential Therapeutic Target for Neurodegeneration and Human Immunodeficiency Virus-Associated Neurocognitive Disorders

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The endoplasmic reticulum (ER) is a multifunctional organelle and serves as the primary site for intracellular calcium storage, lipid biogenesis, protein synthesis, and quality control. Mitochondria are responsible for producing the majority of cellular energy required for cell survival and function and are integral for many metabolic and signaling processes. Mitochondria-associated ER membranes (MAMs) are direct contact sites between the ER and mitochondria that serve as platforms to coordinate fundamental cellular processes such as mitochondrial dynamics and bioenergetics, calcium and lipid homeostasis, autophagy, apoptosis, inflammation, and intracellular stress responses. Given the importance of MAM-mediated mechanisms in regulating cellular fate and function, MAMs are now known as key molecular and cellular hubs underlying disease pathology. Notably, neurons are uniquely susceptible to mitochondrial dysfunction and intracellular stress, which highlights the importance of MAMs as potential targets to manipulate MAM-associated mechanisms. However, whether altered MAM communication and connectivity are causative agents or compensatory mechanisms in disease development and progression remains elusive. Regardless, exploration is warranted to determine if MAMs are therapeutically targetable to combat neurodegeneration. Here, we review key MAM interactions and proteins both *in vitro* and *in vivo* models of Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis. We further discuss implications of MAMs in HIV-associated neurocognitive disorders (HAND), as MAMs have not yet been explored in this neuropathology. These perspectives specifically focus on mitochondrial dysfunction, calcium dysregulation and ER stress as notable MAM-mediated mechanisms underlying HAND pathology. Finally, we discuss potential targets to manipulate MAM function as a therapeutic intervention against neurodegeneration. Future investigations are warranted to better understand the interplay and therapeutic application of MAMs in glial dysfunction and neurotoxicity.

Keywords: mitochondria-associated ER membranes, Unfolded protein response, ER stress, calcium dysregulation, mitochondrial dysfunction, neuropathology, astrocytes

INTRODUCTION

Crosstalk amongst subcellular organelles is an intricate and essential phenomenon for coordinating intracellular communication and ultimately regulating cellular fate. In fact, organelles such as the nucleus, endoplasmic reticulum (ER), golgi apparatus, plasma membrane, mitochondria, lysosomes, peroxisomes and endosomes are now known to both functionally and physically interact with each other to carry out distinct cellular functions (Khan et al., 2019; Liao et al., 2020; Picca et al., 2020). Notably, this review will focus on the direct contact sites between the ER and mitochondria. The ER has many pivotal functions that regulate cellular function and physiology, including calcium (Ca^{2+}) storage and release, lipid biogenesis, and protein folding, assembly, modification and sorting. Moreover, the ER is an intracellular stress sensor, which uses well-established quality control mechanisms such as the unfolded protein response (UPR) and ER-associated degradation (ERAD) signaling pathways to respond to cellular stress and maintain homeostasis (Vincenz-Donnelly and Hipp, 2017). Mitochondria, having often been renowned as the ‘powerhouse of the cell,’ are essential for ATP production, Ca^{2+} buffering as well as regulating various elements of cellular fate through metabolic, apoptotic, and redox signaling (Brand et al., 2013; Friedman and Nunnari, 2014). The direct contact sites between the ER and mitochondria are crucial to regulate both the dynamic structure and function of these two organelles (van Vliet et al., 2014).

MITOCHONDRIA-ASSOCIATED ENDOPLASMIC RETICULUM MEMBRANES

While the first indication of direct ER-mitochondria contact was described in 1956, it took nearly four decades of continued

Abbreviations: α -syn, α -synuclein; A β , amyloid β ; AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; ApoE4, ϵ 4 allele of apolipoprotein E; ANT, adenine nucleotide translocase; APP, amyloid precursor protein; ART, antiretroviral therapy; ATF6, activating transcription factor 6; Bap31, B cell receptor-associated protein 31; BECN1, beclin 1; Ca^{2+} , calcium; ER, endoplasmic reticulum; ETC, electron transport chain; Drp1, dynamin-related protein 1; Fis1, fission 1; FUS, fused in sarcoma; GFAP, glial fibrillary acid protein; gp120, glycoprotein 120; grp75, glucose-regulated protein 75 kDa; GSK-3 β , glycogen synthase kinase-3 β ; HBMEC, human brain microvascular endothelial cells; HEK, human embryonic kidney; HIV-1, human immunodeficiency virus type 1; HAND, HIV-associated neurocognitive disorders; IMM, inner mitochondrial membrane; IP₃R, inositol 1,4,5-triphosphate receptors; IRE1 α , inositol-requiring protein 1 α ; LC3, microtubule-associated protein 1A/1B-light chain 3; MAM, mitochondria-associated ER membrane; MCU, mitochondrial Ca^{2+} uniporter; MEF, mouse embryonic fibroblasts; MFN, mitofusin; Miro, mitochondrial Rho GTPases; mPTP, mitochondrial permeability transitional pore; mtDNA, mitochondrial DNA; OCR, oxygen consumption rate; OMM, outer mitochondrial membrane; Nef, negative factor; OPA1, optic atrophy protein 1; PACS2, phosphofurin acidic cluster sorting 2; PD, Parkinson’s disease; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PGC1 α , proliferator-activated receptor γ coactivator 1 α ; PINK1, phosphatase and tensin homolog-induced putative kinase; PS, presenilin; PTPIP51, protein tyrosine phosphatase-interacting protein 51; ROS, reactive oxygen species; RyR, ryanodine receptors; σ 1R, sigma-1 receptor; Tat, transactivator of transcription; TDP-43, transactive response (TAR) DNA-binding protein 43; TFAM, transcription factor A; UPR, unfolded protein response; VAPB, vesicle-associated membrane protein-associated protein B; VDAC, voltage-dependent anion-selective channel; Vpr, viral protein R.

exploration before the concept of a physical ER-mitochondrial interaction gained acceptance and the term, mitochondria-associated ER membranes (MAMs), was coined (Herrera-Cruz and Simmen, 2017). Following acceptance of this phenomenon, it was not until over 20 years later that we were able to produce the first comprehensive analysis of the MAM proteome (Herrera-Cruz and Simmen, 2017; Janikiewicz et al., 2018; Moltedo et al., 2019). Since these initial investigations, multiple mediators have been identified in regulating both the structure and function of the ER-mitochondrial interface, which are illustrated in **Figure 1**.

Strides have been made in our understanding of how MAMs are integral signaling platforms that regulate multiple cellular functions and maintain homeostasis. In addition to regulating the function and dynamics of both the ER and mitochondria, as discussed below, MAMs are considered central hubs for regulating key cellular processes including apoptosis, autophagy, Ca^{2+} and lipid homeostasis, inflammation, and inflammasome formation (Paillusson et al., 2016; Janikiewicz et al., 2018; Moltedo et al., 2019). Tether proteins between the ER and mitochondria serve as essential scaffolds in regulating MAM-mediated mechanisms whereas communication between these two organelles is primarily facilitated by Ca^{2+} and redox signaling (Marchi et al., 2017; Yoboue et al., 2018; Moltedo et al., 2019).

Briefly, the transfer of Ca^{2+} from the ER to mitochondria is facilitated by inositol 1,4,5-triphosphate receptors (IP₃R) on the ER membrane, voltage-dependent anion-selective channel (VDAC) on the outer mitochondrial membrane (OMM), and cytosolic glucose-regulated protein 75 kDa (grp75), which stabilizes IP₃R and VDAC association within the MAM interface. Notably, cytosolic DJ-1 is newly identified as a critical component in the IP₃R-grp75-VDAC complex (Liu et al., 2019; Basso et al., 2020). On the inner mitochondrial membrane (IMM) mitochondrial Ca^{2+} uniporter (MCU) enables the Ca^{2+} transfer into the matrix, which increases the electrochemical potential and thus oxidative phosphorylation power (Rizzuto et al., 2012; van Vliet et al., 2014; Giorgi et al., 2018). On the ER membrane side of the interface, the sigma-1 receptor (σ 1R) promotes of Ca^{2+} transfer by associating with IP₃R (Hayashi and Su, 2007).

One of the most researched proteins involved in MAM tethering is mitofusin (MFN) 2, which localizes to both the OMM and ER membrane forming a homodimer as well as a heterodimer with MFN1 (de Brito and Scorrano, 2008; Leal and Martins, 2021). However, whether MFN2 positively or negatively regulates MAM tethering remains controversial across differing conditions and cell types (de Brito and Scorrano, 2008; Filadi et al., 2015; Janikiewicz et al., 2018; Moltedo et al., 2019; Leal and Martins, 2021); thus, functional outcomes of MFN2 manipulation can vary. Additional regulators of MAM tethering are vesicle-associated membrane protein-associated protein B (VAPB) on the ER membrane and protein tyrosine phosphatase-interacting protein 51 (PTPIP51) on the OMM (De Vos et al., 2012; Leal and Martins, 2021). Interestingly, MAMs are origin sites for autophagy initiation and autophagosome formation (Yang et al., 2020), which is negatively regulated by VAPB-PTPIP51 tethering (Gomez-Suaga et al., 2017). Finally, MAM tethering *via* ER-associated B cell receptor-associated protein

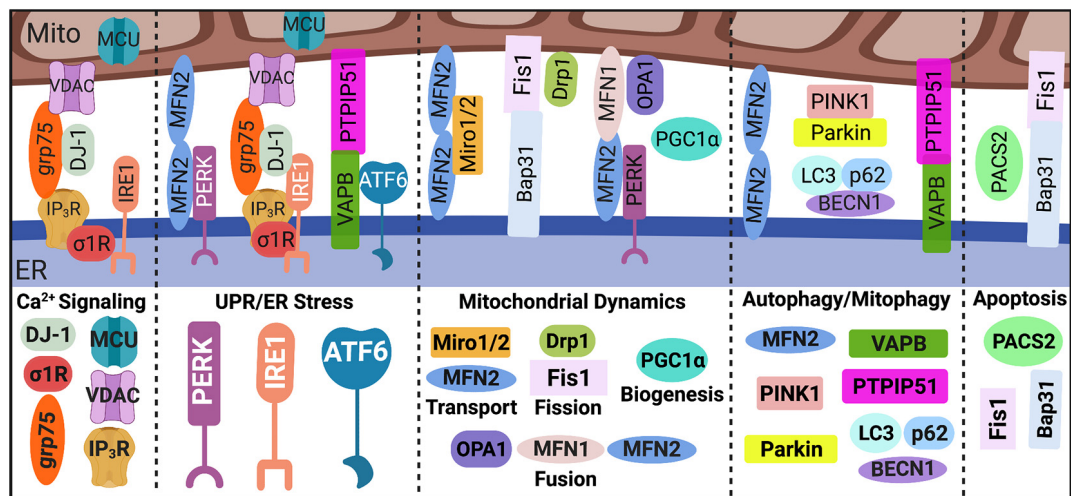


FIGURE 1 | MAM proteome. Direct contact sites between the ER and mitochondria, MAMs, are tightly regulated by key tethering factors: MFN2, VAPB-PTPIP51, IP₃R-grp75-DJ-1-VDAC, and Bap31-Fis1. Mediators within the ER-mitochondrial interface regulate distinct MAM-mediated mechanisms such as Ca²⁺ signaling, UPR/ER stress, mitochondrial dynamics, autophagy/mitophagy, and apoptosis. MAM, mitochondria-associated ER membrane; Mito, mitochondria; ER, endoplasmic reticulum; Ca²⁺, calcium; IP₃R, inositol 1,4,5-triphosphate receptors; VDAC, voltage-dependent anion-selective channel; grp75, glucose-regulated protein 75 kDa; MCU, mitochondrial Ca²⁺ uniporter; σ1R, sigma-1 receptor; UPR, unfolded protein response; PERK, protein kinase RNA-like endoplasmic reticulum kinase; IRE1α, inositol-requiring protein 1α; ATF6, activating transcription factor 6; MFN, mitofusin; Miro, mitochondrial Rho GTPases; Drp1, dynamin-related protein 1; Fis1, fission 1; OPA1, optic atrophy protein 1; PGC1α, proliferator-activated receptor γ coactivator 1α; PINK1, phosphatase and tensin homolog-induced putative kinase; BECN1, beclin 1; LC3, microtubule-associated protein 1A/1B-light chain 3; VAPB, membrane protein-associated protein B; PTPIP51, protein tyrosine phosphatase-interacting protein 51; PACS2, phosphofurin acidic cluster sorting 2; and Bap31, B cell receptor-associated protein 31. Image created with BioRender.com.

31 (Bap31) and mitochondrial fission 1 (Fis1) construct a scaffold for apoptotic signaling (Iwasawa et al., 2011), where phosphofurin acidic cluster sorting 2 (PACS2) is a pivotal regulator (Simmen et al., 2005).

Mitochondria-associated ER membranes are indispensable for ER physiology and health and are intricately involved in cellular responses to UPR/ER stress signaling. Interestingly, many studies have revealed distinct associations between the UPR sensors and MAM regulation both in response to and in the absence of ER stress, highlighting possible non-canonical functions for these proteins (Bravo et al., 2011; van Vliet et al., 2014; Saito and Imaizumi, 2018; van Vliet and Agostinis, 2018). Briefly, there are three arms to the UPR cascade: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring protein 1α (IRE1α), and activating transcription factor 6 (ATF6). PERK is proposed as a key regulator of MAM tethering through direct interaction with MFN2 and is also linked to regulating mitochondrial dynamics and bioenergetics (Verfaillie et al., 2012; Munoz et al., 2013; Rainbolt et al., 2014; van Vliet and Agostinis, 2016; Lebeau et al., 2018; Balsa et al., 2019). IRE1α, which is commonly associated with cellular responses to infections or inflammation, is implicated in ER-mitochondrial Ca²⁺ transfer, mitochondrial respiration and redox homeostasis through associations with IP₃R (Son et al., 2014; Carreras-Sureda et al., 2019) and/or σ1R (Mori et al., 2013). ATF6 is shown to both interact with and be regulated by the key MAM tethering protein VAPB (Gkogkas et al., 2008). Moreover, ATF6 can regulate lipid biosynthesis and ER expansion suggesting a possible interplay in MAM-mediated lipid homeostasis and

ER-mitochondrial physiology (Bommasiamy et al., 2009). Most recently, ATF6 has also been implicated in ER-mitochondrial Ca²⁺ homeostasis (Burkewitz et al., 2020).

The ER and mitochondria contact sites are fundamental for regulating mitochondrial function, dynamics, and homeostasis. For example, Ca²⁺ and redox signaling between the ER and mitochondria are essential for regulating mitochondrial integrity and bioenergetic activity. Moreover, mitochondrial dynamics are regulated by a balance between fission and fusion both of which are coordinated by the ER-mitochondrial interface. In fact, fission requires the physical maneuvering of the ER membrane to constrict around the mitochondrion fission site which then recruits the primary regulator of mitochondrial fission: dynamin-related protein 1 (Drp1), along with fission adaptor proteins, mitochondrial fission factor and Fis1 (Friedman et al., 2011; Moltedo et al., 2019). Fusion of mitochondria require the involvement of MFN1 and MFN2 which, as aforementioned, are enriched at MAMs and regulate MAM tethering (Moltedo et al., 2019). Notably, MFN1/2 coordinated OMM fusion while optic atrophy protein 1 (OPA1) mediated IMM fusion.

Beyond fission and fusion, biogenesis and degradation are also vital for ensuring healthy mitochondria turnover. Following mitochondrial fission events, damaged mitochondria are removed *via* mitophagy, in which phosphatase and tensin homolog-induced putative kinase (PINK1) and beclin 1 (BECN1) at the MAM interface promote autophagosome formation (Gelmetti et al., 2017). Notably, PINK1 phosphorylates MFN2 leading to Parkin recruitment and initiation of mitophagy machinery while proteins such as p62 and

microtubule-associated protein 1A/1B-light chain 3 (LC3) coordinate cargo selection and autophagosome/mitophagosome maturation (Molledo et al., 2019; Yang et al., 2020). Meanwhile, biogenesis is a self-renewal process in which mitochondrial machinery is 'replenished' by increased transcription and translation of mitochondrial DNA (mtDNA) as well as increased synthesis, import, and assembly of nuclear DNA-encoded mitochondrial proteins (Popov, 2020). While the role of MAMs in mitochondrial biogenesis is not clear, expression of proliferator-activated receptor γ coactivator 1 α (PGC1 α), a master regulator of mitochondrial biogenesis, controls ER-mitochondrial contact. Notably, PGC1 α knockout perturbs MAM contact while overexpression promotes increased interaction (Ciron et al., 2015). Finally, mitochondrial transport is essential to ensure mitochondria are distributed to meet the energetic demands of a cell. Trafficking of mitochondria is facilitated by mitochondrial Rho GTPases (Miro), which directly interact with MFN1/2 and regulate ER-mitochondrial contact (Misko et al., 2010, 2012; Modi et al., 2019). Moreover, functional MFN2 is required for mitochondrial mobility (Misko et al., 2010, 2012).

MITOCHONDRIA-ASSOCIATED ENDOPLASMIC RETICULUM MEMBRANES IN NEUROPATHOLOGY

Given the importance of MAM-associated mechanisms in cellular homeostasis, MAMs are gaining attention as plausible pathological platforms underlying the development and/or progression of disease (Pinton, 2018). Briefly, the role of MAMs in neuropathology, which have been previously reviewed (Raeisossadati and Ferrari, 2020; Wilson and Metzakopian, 2020; Leal and Martins, 2021), have primarily been centered on neurons, highlighting MAMs as pivotal regulators of synaptic transmission and neuronal health (Bernard-Marissal et al., 2018; Gomez-Suaga et al., 2019; Shirokova et al., 2020; Leal and Martins, 2021). Astrocyte MAMs are largely a new exploration. Notably, enrichment of MAMs in astrocyte endfeet may be crucial for regulating the blood-brain interface and brain healing following injury (Bergami and Motori, 2020; Gbel et al., 2020). Moreover, knockdown of MAM-associated proteins, PACS2 or σ 1R, induces degeneration of hippocampal neurons and astrocytes, supporting the importance of MAMs for neural cell survival (Hedskog et al., 2013). The presence and function of MAMs in other neural cells, microglia and oligodendrocytes, remain unconfirmed (Bernard-Marissal et al., 2018; Shirokova et al., 2020).

Many of the cellular processes that are implicated in the etiology of neurodegenerative diseases are coordinated at the ER-mitochondrial interface such as dysregulated lipid and Ca^{2+} homeostasis, mitochondrial dysfunction, ER and oxidative stress, impaired autophagy, and inflammation. Neurons are particularly susceptible to mitochondrial dysfunction given the high energetic demand of brain tissue (Grimm and Eckert, 2017; Picca et al., 2020). Moreover, ER stress is induced by the aggregation of misfolded proteins, which is a physical hallmark

of most neurodegenerative pathologies. Formation of protein aggregates can be a consequence of increased production of misfolded proteins (ER dysfunction), the impaired removal of dysfunctional proteins (impaired autophagy), or both (Sweeney et al., 2017; Monaco and Fraldi, 2020). Regardless, ER stress and mitochondrial dysfunction are increasingly being proposed as key therapeutic targets for combating neuropathology, with MAMs arising as the essential crossroad for this collaboration. It is worth considering whether these central hubs can be manipulated to reconcile cellular dysfunction and degeneration and to restore CNS homeostasis.

Beyond the classic hallmarks of neuropathology in the context of known MAM-associated functions, dysregulation of MAM tethering and activity are implicated in a number of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). However, whether these MAM alterations arise as intended remedial responses or are the causative agents in these disease pathologies remains to be determined. The distinct interplay of MAMs in these neuropathological conditions is illustrated in **Figure 2** and discussed below.

Alzheimer's Disease

As one of the most common forms of dementia, Alzheimer's disease is characterized by the aggregation of extracellular amyloid β ($A\beta$) peptides and intracellular hyperphosphorylated tau proteins, termed plaques and tangles, respectively. Treatment with $A\beta$ in primary hippocampal neurons increased expression of MAM-associated PACS2 and σ 1R proteins, as well as direct ER-mitochondrial contact *via* the IP₃R-VDAC bridging complex. Expression of PACS2 and σ 1R was also increased in the hippocampus, cortex, and cerebellum brain regions of a potent amyloid precursor protein (APP) mutant AD mouse model. However, in human AD postmortem cortical tissues, PACS2 increased, but σ 1R expression decreased (Hedskog et al., 2013). Interestingly, MAMs serve as a key production site for $A\beta$ peptides (Schreiner et al., 2015). The formation of $A\beta$ plaques occurs following the catalytic processing of APP by the γ -secretase complex. Two major components of this complex, presenilin (PS) 1 and PS2, localize to the ER-mitochondria interface and modulate MAM functions, specifically lipid and Ca^{2+} homeostasis (Area-Gomez et al., 2009; Zampese et al., 2011; Area-Gomez et al., 2012; Galla et al., 2020). Notably, overexpressing PS2 increases both ER-mitochondria contact and Ca^{2+} transfer from the ER to mitochondria (Zampese et al., 2011; Galla et al., 2020). This phenomenon appears to be mediated through interactions between PS2 and MFN2 (Filadi et al., 2016). Furthermore, silencing MFN2 in human embryonic kidney (HEK) 293 cells stably expressing an APP mutant to overproduce $A\beta$, increased MAM contact and Ca^{2+} transfer, which impairs γ -secretase maturation and activity, ultimately decreasing $A\beta$ production (Leal et al., 2016). Leal et al. also recently reported decreased expression of MFN1/2 in postmortem human AD brain tissues. They further confirmed a positive correlation between $A\beta$ and MAM contact in multiple AD mouse models and *in vitro* neuron cultures exposed to $A\beta$. The increased connectivity between ER and mitochondria in response to $A\beta$

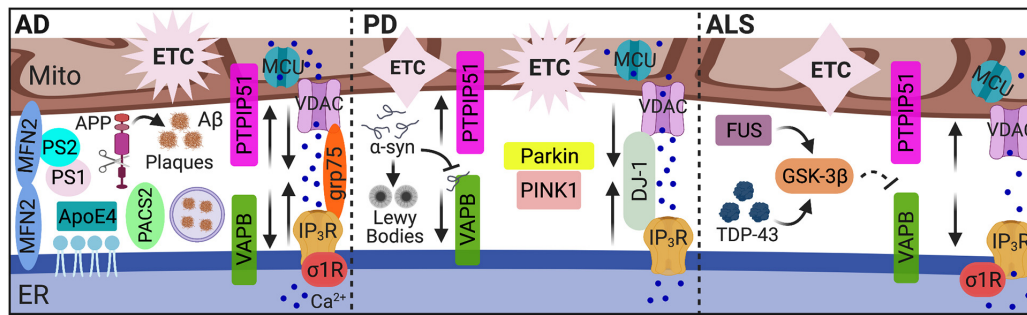


FIGURE 2 | MAMs in AD, PD, and ALS. While dysregulated MAM-associated mechanisms are hallmarks of neurodegenerative pathology, the unique pathological features of AD, PD, and ALS alter MAM contact and communication emphasizing MAMs as pivotal players in neuropathology. In AD, MAM contact, Ca^{2+} transfer, and MAM-mediated mechanisms (i.e., autophagy) are increased among *in vitro* and mouse models, yet decreased MAM-mediator expression and interaction was found in human AD cortical tissues. In PD, both increased and decreased ER MAM contact and communication were reported. In ALS, MAM tethering and Ca^{2+} transfer were significantly impaired. MAMs, mitochondria-associated ER membranes; Mito, mitochondria; ER, endoplasmic reticulum; AD, Alzheimer's disease; $\text{A}\beta$, amyloid β ; APP, amyloid precursor protein; ApoE4, $\epsilon 4$ allele of apolipoprotein E; PS, presenilin; MFN, mitofusin; PACS2, phosphofurin acidic cluster sorting 2; Ca^{2+} , calcium; IP₃R, inositol 1,4,5-triphosphate receptors; VDAC, voltage-dependent anion-selective channel; grp75, glucose-regulated protein 75 kDa; MCU, mitochondrial Ca^{2+} uniporter; $\sigma 1\text{R}$, sigma-1 receptor; ETC, electron transport chain; PD, Parkinson's disease; α -syn, α -synuclein; VAPB, vesicle-associated membrane protein-associated protein B; PTPIP51, protein tyrosine phosphatase-interacting protein 51; PINK1, phosphatase and tensin homolog-induced putative kinase; ALS, amyotrophic lateral sclerosis; TDP-43, transactive response (TAR) DNA-binding protein 43; GSK-3 β , glycogen synthase kinase-3 β ; and FUS, fused in sarcoma. Image created with BioRender.com.

subsequently increased mitochondrial metabolic function and autophagosome formation, likely to promote removal of $\text{A}\beta$ aggregates (Leal et al., 2020). Of note, another recent examination of human AD cortical tissues showed a decreased expression and interaction of MAM tether proteins, VAPB and PTPIP51, in addition to decreased IP₃R expression. The decreased expression of these proteins also correlated with increased disease stage severity (Lau et al., 2020). Thus, decreased expression of MAM-mediators in human AD tissues was reported across three separate studies (Hedskog et al., 2013; Lau et al., 2020; Leal et al., 2020) suggesting impaired ER-mitochondrial tethering, highlighting unique differences between animal models and human tissues. Regardless, these findings strongly implicate MAMs as possible targets to combat AD/ $\text{A}\beta$ pathology.

Disease-associated tau protein alters mitochondrial transport, dynamics, bioenergetics and degradation (reviewed by Szabo et al., 2020). These findings further discuss the implications of MAMs in tau pathology as only two studies have so far explored this phenomenon; both of these models identified increased ER-mitochondrial contact during tau pathology (Perreault et al., 2009; Cieri et al., 2018). The $\epsilon 4$ allele of apolipoprotein E (ApoE4) significantly associates with an increased risk for sporadic AD. Treatment of astrocyte conditioned media cultured from ApoE4 knock-in mice, upregulated MAM activity in human fibroblasts and mice neurons, as measured by the synthesis of phospholipids and cholesteryl esters (Tambini et al., 2016). This outcome was averted when repeated in mouse embryonic fibroblasts (MEF) harboring MFN2 knockout, which in this model, decreased MAM tethering (de Brito and Scorrano, 2008; Tambini et al., 2016).

Parkinson's Disease

Parkinson's disease is a neurodegenerative disease manifesting with primarily motor deficits due to damaged and degenerative

dopaminergic neurons in the substantia nigra. A key pathophysiology underlying PD is the presence of 'Lewy bodies' comprised of α -synuclein (α -syn) aggregates. However, tau pathology is also present in some cases. PD pathology is characterized by a number of MAM-associated cellular processes including impaired autophagy, Ca^{2+} homeostasis, lipid metabolism, ER stress, and mitochondrial dynamics (reviewed by Rodriguez-Arribas et al., 2017; Gomez-Suaga et al., 2018). Notably, overexpression or silencing of α -syn confirms regulation on mitochondrial dynamics, ER-mitochondrial coupling and Ca^{2+} transfer (Cali et al., 2012; Guardia-Laguarta et al., 2014). However, these findings are also inconsistent as one demonstrates increased organelle contact while the other reports disruption in tethering. From a more recent report, α -syn binds to VAPB on the ER membrane, disrupting interaction with PTPIP51 on the OMM and subsequently, MAM tethering, Ca^{2+} transfer, and ATP production (Paillusson et al., 2017). Thus, the effects of α -syn on MAM function are linked to impaired bioenergetic activity.

Another MAM connection to the neuropathology of PD involves PINK1 and Parkin. Mutations in PINK1 and Parkin are key risk factors for the development of PD. The functions of these proteins are critical in maintaining mitochondrial health by regulating mitochondrial biogenesis, degradation, dynamics, function, and transport. PINK1 and Parkin localize to MAMs, which is not surprising given their prominent roles in mitophagy and MAMs being the site for mitochondrial fission (Gomez-Suaga et al., 2018). Moreover, Parkin is implicated as a possible regulator for MAM tethering although controverting evidence has been reported as to whether it is a positive or negative regulator (Cali et al., 2013; Gautier et al., 2016). Briefly, overexpression of Parkin in both HeLa and a neuroblastoma cell line enhanced MAM coupling and Ca^{2+} transfer to increase ATP production (Cali et al., 2013). Expression of Parkin is encoded

by the *PARK2* gene. Increased mitochondrial-ER contact was found in fibroblasts from a *PARK2* knockout mouse and PD patients with *PARK2* mutation (Gautier et al., 2016). Moreover, mutations in the gene for DJ-1, which as mentioned above has been identified as a novel component in the IP₃R-grp75-VDAC complex, are causative for autosomal recessive familial PD. The DJ-1 protein has been identified to have a protective role in oxidative stress and modulates mitochondrial morphology. Similar to a report on α -syn, overexpression of DJ-1 enhances ER-mitochondrial coupling and Ca²⁺ transfer while silencing of DJ-1 impairs mitochondrial Ca²⁺ flux and induces fragmentation (Ottolini et al., 2013). All these findings highlight the importance of MAMs as regulators of mitochondrial function and physiology in the context of PD pathology.

Amyotrophic Lateral Sclerosis

A key component of ALS pathology is deposits of transactive response (TAR) DNA-binding protein 43 (TDP-43). Like α -syn, TDP-43 alters MAM tethering and Ca²⁺ homeostasis by interrupting the relationship between VAPB and PTPIP51. However, the mechanism of disruption is instead mediated through activation of glycogen synthase kinase-3 β (GSK-3 β) (Stoica et al., 2014). Interestingly, accumulation of fused in sarcoma (FUS), a key pathological feature characterizing ALS, also interrupts VAPB and PTPIP51 association and MAM tethering *via* GSK-3 β activation (Stoica et al., 2016). This interruption was accompanied by compromised mitochondrial Ca²⁺ uptake and ATP production. Thus, ALS pathology is characterized by two factors that activate GSK-3 β to disentangle the MAM interface; however, the target of GSK-3 β to facilitate this interference remains unknown. The significance of MAM tethering in ALS pathology is further supported as a P56S mutation in VAPB is causative of ALS (Nishimura et al., 2004). Moreover, mutation or perturbed function of another MAM protein, σ 1R, which is essential for Ca²⁺ transfer from the ER to mitochondria, is a causal agent to ALS pathology and motor neuron degeneration (Al-Saif et al., 2011; Bernard-Marissal et al., 2015). Additional implications and associations of MAMs in ALS pathology are previously reviewed (Manfredi and Kawamata, 2016; Lau et al., 2018).

HUMAN IMMUNODEFICIENCY VIRUS-ASSOCIATED NEUROCOGNITIVE DISORDERS

Human immunodeficiency virus type 1 (HIV-1) can invade the CNS early during infection and infect residential glial cells (astroglia, microglia, and oligodendrocytes) where infection can persist for life. Even with the medical advancement of antiretroviral therapy (ART), low viral replication, chronic neuroinflammation, glial dysfunction, and HIV-1 protein toxicity contribute to the development of a spectrum of HIV-associated neurocognitive disorders (HAND). In fact, HAND continue to afflict approximately 30–70% of people living with HIV, depending on cohort demographics (Simioni et al., 2010;

Heaton et al., 2011). HAND are characterized by different levels of cognitive impairments and interference with one's daily functioning. At the extreme end of the spectrum, symptoms clinically manifest as dementia (Mackiewicz et al., 2019).

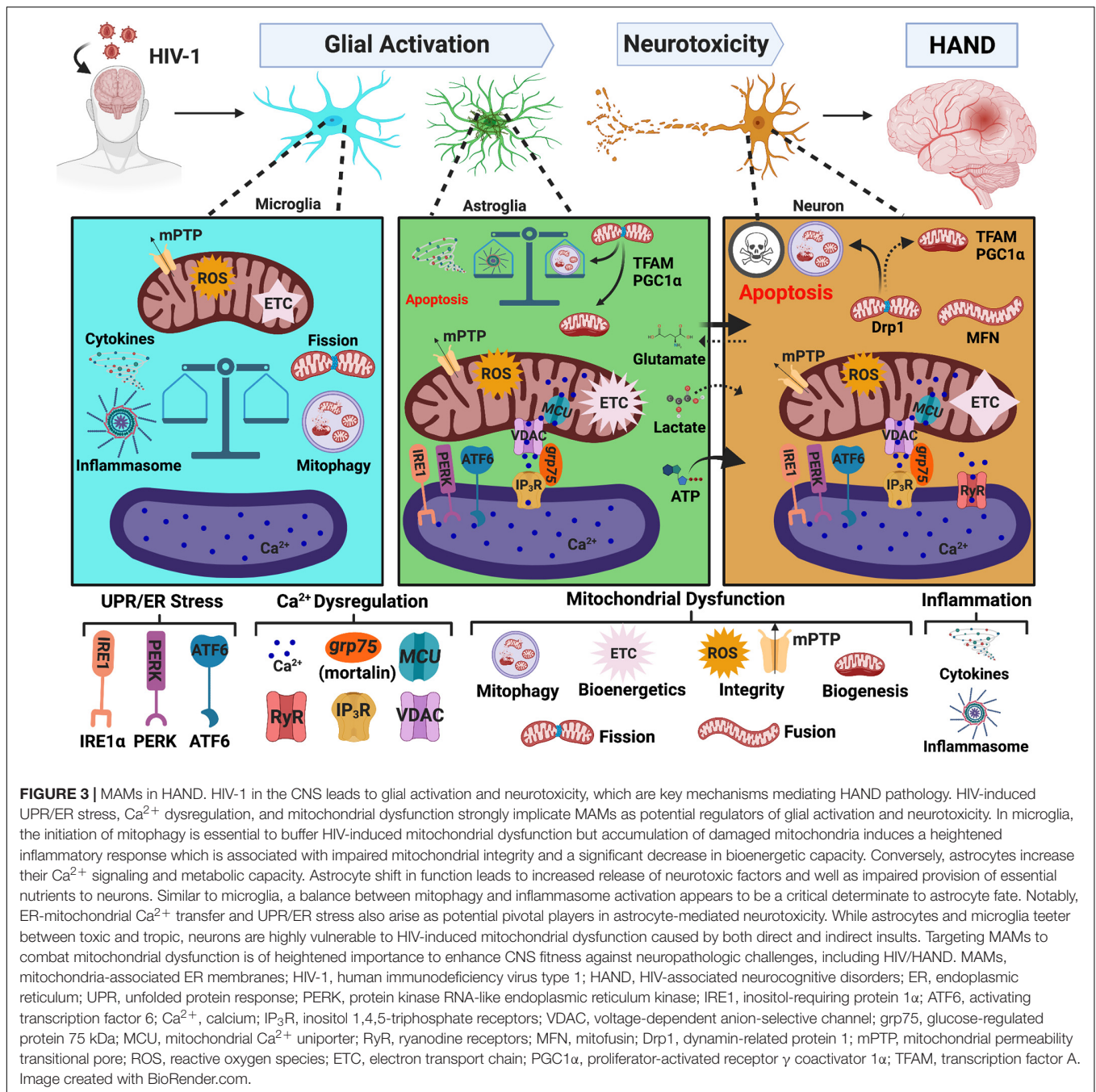
The pathology of HIV-1 infection often includes "accelerated aging." Thus, HIV-1 patients are more prone to developing early onset symptoms for a number of age-related diseases including the neurodegenerative pathologies discussed above (Robertson et al., 2007; Cody and Vance, 2016; Wang et al., 2017; Mackiewicz et al., 2019). In fact, A β plaques as well as tauopathy can both associate with and be exacerbated by HAND pathology (Kim et al., 2013; Brown et al., 2014; Hategan et al., 2019). Of note, the primary HIV-1 proteins implicated in neurotoxicity are transactivator of transcription (Tat), glycoprotein (gp)120, viral protein R (Vpr), and negative factor (Nef). Moreover, ART drugs are now identified as key contributors to the cellular senescence and accelerated aging underlying HIV/HAND pathology, which was reviewed previously with an emphasis on mitochondrial dysfunction (Schank et al., 2021).

Khan et al. (2019) recently published insights into potential inter-organelle collaborations in HIV/HAND pathogenesis. Despite obvious disruptions in ER and mitochondrial homeostasis in HAND pathology, there remains limited investigations and/or considerations of MAMs (Ma et al., 2016; Nooka and Ghorpade, 2017; Khan et al., 2019). Below we discuss the implications of MAMs in HAND pathology by reviewing the effects of HIV-1 on ER stress, Ca²⁺ dysregulation and mitochondrial dysfunction, which is also illustrated in **Figure 3**. Together, these findings strongly support altered MAM signaling as a prominent contributor to HAND pathology.

Human Immunodeficiency Virus-1 and Endoplasmic Reticulum Stress

As aforementioned, ER stress is a key characteristic in neurodegenerative pathologies, and MAMs are intricately involved in cellular responses to ER stress. Indeed, the three UPR arms are now increasingly considered integral mediators within the MAM proteome (van Vliet and Agostinis, 2016, 2018; Saito and Imaizumi, 2018; Malli and Graier, 2019). In the context of HAND, significant increases in ER stress markers are detected in the frontal cortex of brain tissues from HIV-1 positive individuals. In fact, the levels of ER stress positively correlate with cognitive decline, wherein the most severe cases of HAND have the highest expression of ER stress markers (Lindl et al., 2007; Akay et al., 2012). Interestingly, these studies show that while ER stress is evident in both neurons and astrocytes, astrocytes appear to have higher expression of ER stress markers. These findings do not necessarily mean neurons are less likely to endure ER stress during HIV-1 infection. Rather, astrocytes may be more resilient to prolonged ER stress, and neurons could be more susceptible to succumb to apoptosis.

It is well-known that during neurodegenerative or neuroinflammatory conditions, astrocytes become 'activated', shifting their function from neurotrophic to a more neurotoxic phenotype. Astrocyte-mediated neurotoxicity has arisen



as a key feature in HAND pathology with UPR/ER stress as a potential regulator (Fan and He, 2016; Shah et al., 2016; Nooka and Ghorpade, 2017, 2018; Natarajaseenivasan et al., 2018). In fact, while HIV-1-induced ER stress has not yet been extensively investigated, most investigations are primarily centered around astrocytes. Notably, expression of HIV-1 Tat in astrocytes induces aggregation of glial fibrillary acid protein (GFAP). Both Tat expression and GFAP aggregation activate the three UPR pathways (Fan and He, 2016). HIV-1 gp120 specifically activates the IRE1α branch of UPR signaling in an astrocyte cell line,

primary human astrocytes, and astrocyte-restricted gp120 transgenic mice, which is linked to the initiation of apoptotic signaling (Shah et al., 2016). Inhibition of ER stress or UPR signaling in both of these studies reverses astrocyte-mediated neurotoxicity and apoptotic signaling (Fan and He, 2016; Shah et al., 2016). Moreover, studies from our lab demonstrate induction of the three UPR pathways in primary human astrocytes in response to HAND-relevant stimuli (whole HIV-1, inflammation, and ART drugs), which associate with mitochondrial depolarization (Nooka and Ghorpade, 2017). HIV-1 Tat-induced ER stress in a CD4+ T cell line

(Campestrini et al., 2018) neurons (Norman et al., 2008) and human brain microvascular endothelial cells (HBMEC) (Ma et al., 2016) are also accompanied by changes in mitochondrial function and apoptotic signaling supporting cooperation of the ER and mitochondria during HIV/HAND pathology. Indeed, inhibition of ER stress reversed HIV-1-induced mitochondrial dysfunction and increased cell viability in HBMEC (Ma et al., 2016). These findings not only implicate MAMs in HAND pathology but also emphasize UPR/ER stress signaling as an important regulator of mitochondrial function, cellular fate and astrocyte-mediated neurotoxicity.

Human Immunodeficiency Virus-1 and Ca²⁺ Dysregulation

As discussed above, the ER is the primary site for intracellular Ca²⁺ storage, and MAMs are hubs for regulating Ca²⁺ homeostasis. HIV-1 modulates Ca²⁺ signaling and perturbs Ca²⁺ homeostasis. Many of these studies have been previously reviewed or discussed (Haughey and Mattson, 2002; Hu, 2016; Fields and Ellis, 2019). Altered Ca²⁺ dynamics during HIV-1 exposure is directly linked to apoptotic signaling, UPR induction, and impaired mitochondrial integrity, energetics, and/or quality control thus implicating Ca²⁺ dysregulation as a key component in HIV-1-induced neurotoxicity and astrogliosis. One of the earliest studies identifying this relationship was in rat hippocampal neurons exposed to HIV-1 Tat, which induced apoptosis through the elevation of cytoplasmic Ca²⁺ and increased mitochondrial Ca²⁺ uptake. Chelating cytosolic Ca²⁺ or pharmacological inhibiting mitochondrial Ca²⁺ uptake *via* MCU protected neurons from HIV-1 Tat-mediated neurotoxicity (Kruman et al., 1998). Interestingly, a later study in rat cortical neurons linked ER and mitochondrial Ca²⁺ loss *via* ryanodine receptors (RyR) as an upstream mechanism for HIV-1 Tat-mediated UPR induction and mitochondrial hyperpolarization (Norman et al., 2008). While less prominent, Ca²⁺ mobilization is also implicated in HIV-1 gp120-(Meeker et al., 2016) and Vpr-(Jones et al., 2007) mediated neurotoxicity, which associated with impaired axonal mitochondria transport and apoptotic signaling, respectively.

In the context of astrocytes, our previous studies indicate a pivotal role of Ca²⁺ signaling in regulating ER stress and mitochondrial dysfunction induced by HAND-relevant stimuli (whole HIV-1, inflammation, and ART drugs). Notably, chelation of cytoplasmic Ca²⁺ was able to reverse HIV-1-induced ER stress and mitochondrial depolarization (Nooka and Ghorpade, 2017). Moreover, knockdown of MCU to reduce mitochondrial Ca²⁺ uptake during exposure to HIV-1 Tat and/or cocaine reverses astrocyte mitochondrial dysfunction and metabolic switching to restore a neuroprotective phenotype (Natarajaseenivasan et al., 2018). Manipulation of VDAC1 (the OMM Ca²⁺ channel within the MAM interface) or “mortalin” (aka grp75, the scaffolding protein between IP₃R on the ER membrane and VDAC on the mitochondria) is also able to rescue neurons from HIV-1 Tat-induced astrocyte-mediated neurotoxicity (Fatima et al., 2017; Priyanka et al., 2020). Specifically, HIV-1 Tat expressing

primary human astrocytes trigger neuronal death by excessive ATP release, a mechanism that was counteracted by repression of VDAC1 (Fatima et al., 2017). Neuroinflammation and glutamate excitotoxicity are additional mechanisms for which astrocytes inflict neuronal damage during HAND, as previously reviewed by our research team (Cisneros and Ghorpade, 2012; Borgmann and Ghorpade, 2015). Overexpression of mortalin/grp75 protects neurons from astrocyte-mediated neurotoxicity by reversing HIV-1 Tat-induced astrocyte mitochondrial dysfunction and fragmentation while also reducing the release of excess ATP, inflammatory cytokines, and extracellular glutamate (Priyanka et al., 2020). Altogether, these findings strongly support MAM-mediated Ca²⁺ transfer as a pivotal regulator of astrocyte-mediated neurotoxicity during HAND pathogenesis.

It is also noteworthy to mention, that while research with HIV-1 Nef is less investigated in HAND pathogenesis, it is known to play a prominent role for Ca²⁺ dysregulation in T cells (Manninen and Saksela, 2002; Shelton et al., 2012; Silva et al., 2016). In fact, HIV-1 Nef directly interacts with both mortalin/grp75 (Shelton et al., 2012) and IP₃R (Manninen and Saksela, 2002), which are key mediators in ER to mitochondria Ca²⁺ transfer. Thus, there is likely an interplay between HIV-1 Nef and the MAM interface. More studies are needed to determine the role of HIV-1 Nef and Ca²⁺ dysregulation in neural cells.

Human Immunodeficiency Virus-1 and Mitochondrial Dysfunction

The MAMs are essential for regulating mitochondrial function and homeostasis. Defects in mitochondrial bioenergetics, biogenesis, degradation, dynamics, integrity and transport are all present in the pathology of HAND and are discussed below. The role of mitochondrial dysfunction in HIV/HAND pathology is rapidly gaining attention with two recent reviews by Fields and Ellis (2019) and Schank et al. (2021); however, neither discuss the potential interplay of MAMs. It is well established that HIV-1 can induce neuronal apoptosis, in which mitochondria [and MAMs] are known upstream regulators through Ca²⁺ and redox signaling (Kruman et al., 1998; van Vliet et al., 2014; Marchi et al., 2017). In addition to regulating apoptosis, Ca²⁺ and redox signaling between mitochondria and ER are also essential for regulating mitochondrial integrity and bioenergetic activity, autophagy and inflammasome activation (van Vliet et al., 2014), again highlighting the importance of ER-mitochondrial inter-organelle collaboration in negotiating cellular fate.

In human neurons, exposure to HIV-1 Tat and Vpr decreased VDAC (OMM Ca²⁺ transporter) protein expression, dysregulated RNA expression of several genes regulating mitochondrial metabolism and decreased ATP levels (Darbinian et al., 2020). These findings were also associated with mtDNA damage, reactive oxygen species (ROS) accumulation, increased expression apoptotic proteins, and release of cytochrome C, emphasizing the relationship of mitochondrial bioenergetics and integrity. Less clear are the effects of HIV-1 on neuronal mitochondrial dynamics, which vary greatly across investigations. Two separate studies looking at the brain

tissues from HIV + donors with or without HIV encephalitis, specifically centered on neurons, report enlarged mitochondria as a unique pathological feature of HAND (Avdoshina et al., 2016; Fields et al., 2016).

Changes in mitochondrial morphology associated with increased expression of fusion proteins (MFN1 and OPA1) and decreased expression and/or activation of mitochondrial fission proteins (Fis1 and Drp1). Interestingly, as previously discussed with ER stress markers, decreased expression of mitochondrial Drp1 also coincided with increased HIV-associated neurocognitive decline (Fields et al., 2016). Similar disruptions on mitochondrial morphology were confirmed in gp120 transgenic mice and by gp120 treatment to neuronal cell cultures (Avdoshina et al., 2016; Fields et al., 2016). These reports also found increased extracellular acidification rate indicating increased glycolysis (Fields et al., 2016) and reduced oxygen consumption rate (OCR) (Avdoshina et al., 2016) suggesting a deviation in mitochondrial bioenergetics. Noteworthy, overexpressing Drp1 reverses gp120-mediated neuronal mitochondrial dysfunction reducing both neuroinflammation and neurodegeneration (Fields et al., 2016). These findings suggest mitochondrial fission as a potential therapeutic mechanism to combat HIV-mediated mitochondrial dysfunction in neurons.

On the contrary, more recent studies by Teodorof-Diedrich and Spector (2018) looking at the effects of both HIV-1 gp120 and Tat on mitochondrial dynamics in human neurons and Rozzi et al. (2018) looking at the effects of HIV-1 Tat in rat cortical neurons, instead identified a proclivity toward mitochondrial fission and fragmentation. In fact, increased Drp1 expression, activity, and/or translocation were critical for these outcomes. Both studies also reported impaired mitochondrial integrity as demonstrated by decreased membrane potential ($\Delta\Psi_m$). Noteworthy, Teodorof-Diedrich and Spector (2018) also found an increased recruitment of mitophagy proteins (Parkin, p62, and LC3) and mitophagosome formation, yet an impaired mitophagic flux leading to accumulation of damaged mitochondria due to incomplete mitophagy. The discrepancy regarding HIV-1 gp120 on neuronal mitochondrial dynamics may be attributed to different *in vitro* models as the prior two studies were in rodents (Avdoshina et al., 2016; Fields et al., 2016) and the later in primary human neurons (Teodorof-Diedrich and Spector, 2018). Moreover, there may be general discrepancies between the effects of HIV-1 gp120 versus HIV-1 Tat. Regardless, the identical findings of elongated mitochondria in neurons of HIV+ brain tissues remain a significant find.

However, there is one similarity across these four studies in regard to mitochondrial distribution/localization. There appears to be an overall decrease in mitochondrial trafficking throughout the processes with increased aggregation of mitochondria near the soma. Impaired mitochondria axonal transport is also evident in neurons exposed to HIV-1 Vpr, which was further associated with decreased ATP production and increased expression of senescent markers (Wang et al., 2017). As mitochondria are essential for synaptic maintenance and to meet the energetic demands for neurotransmission, disrupted axonal mitochondria transport arises as a potential key pathological feature in HAND

and age-related axonal degeneration. Interestingly, although HIV-1 Vpr is primarily known as a nuclear protein, it also directly interacts with adenine nucleotide translocase (ANT) on the OMM, which is a key regulator of mitochondrial integrity *via* formation of the mitochondrial permeability transitional pore (Huang et al., 2012; Wang et al., 2017; Cowan et al., 2019). In fact, inhibiting the interaction between HIV-1 Vpr and ANT was able to reverse deficits in mitochondrial trafficking (Wang et al., 2017). Finally, this study also suggests HIV-1 Vpr may disrupt mitochondrial biogenesis in neurons *via* reduction of PGC1 α expression. Swinton et al. (2019) confirmed decreased expression of PGC1 α in HIV+ brain cortical tissues as well as decreased transcription factor A (TFAM), another regulator of mitochondrial biogenesis (Swinton et al., 2019).

In astrocytes, both HIV-1 infection and external HIV-1 exposure perturb mitochondrial integrity (Nooka and Ghorpade, 2017; Natarajaseenivasan et al., 2018; Ojeda et al., 2018; Priyanka et al., 2020). Unlike neurons, astrocytes increase their metabolic activity and ATP production (Natarajaseenivasan et al., 2018; Swinton et al., 2019). Moreover, while neurons have decreased TFAM expression in HIV+ brain tissues, astrocytes have increased TFAM expression (Swinton et al., 2019). The increased metabolic and mitochondrial biosynthetic profile may be a key feature underlying astrocyte activation and astrocyte-mediated neurotoxicity during HAND. For example, HIV-1 Tat provokes astrocytes to undergo a distinct metabolic shift from glucose to fatty acid oxidation, which restricts astrocyte provision of lactate to neurons (Natarajaseenivasan et al., 2018). In addition to decreasing release of neurotrophic factors when 'activated' by HIV-1 Tat, astrocytes increase their release of neurotoxic factors including excessive ATP (Fatima et al., 2017; Priyanka et al., 2020), ROS (Natarajaseenivasan et al., 2018; Priyanka et al., 2020), and inflammatory cytokines (Natarajaseenivasan et al., 2018). As briefly discussed in the previous section, blocking ER-mitochondrial Ca²⁺ transfer *via* VDAC (on the OMM) (Fatima et al., 2017), MCU (on the IMM) (Natarajaseenivasan et al., 2018), or mortalin/grp75 (scaffold between IP₃R and VDAC) (Priyanka et al., 2020) restored an astrocyte neurotrophic phenotype, highlighting a probable MAM interplay in astrocyte-mediated neurotoxicity during HAND. Moreover, HIV-1 infection (Ojeda et al., 2018) or HIV-1 Tat expression (Priyanka et al., 2020) in astrocytes induced mitochondrial fragmentation, which may be followed by defective mitophagy, similar to what was seen by Teodorof-Diedrich and Spector (2018) in neurons. Notably, accumulation of damaged mitochondria promoted inflammasome activation, which was subsequently followed by cell death (Ojeda et al., 2018). However, astrocytes that had successful mitophagy, were able to attenuate mitochondrial dysfunction and resist cell death. The divergence between these fates appeared dependent on the mode of infection, where productively infected astrocytes favored survival, and non-productive infection succumbed to inflammasome-mediated cell death.

Mitochondrial dysfunction in microglia has been less studied; however, there is a recent review discussing the important role of microglia in HAND (Borrajo et al., 2021). Similar to astrocytes, there appears to be a delicate balance

between mitophagy and inflammasome formation underlying microglia activation during HAND (Thangaraj et al., 2018; Rawat et al., 2019). In response to HIV-1 Tat (Thangaraj et al., 2018) or ssRNA (Rawat et al., 2019), there is increased expression of autophagy/mitophagy proteins (PINK1, Parkin, p62, LC3, and BECN1) with a subsequent blockade of mitophagy flux, leading to the accumulation of mitophagosomes and damaged mitochondria. These changes are associated with increased ROS generation and impaired mitochondrial integrity (Rawat et al., 2019). However, unlike astrocytes, there is a significant decrease in mitochondrial bioenergetic activity (Thangaraj et al., 2018). Importantly, defects in mitophagy appear to be central to microglial activation and inflammasome formation (Thangaraj et al., 2018; Rawat et al., 2019). Indeed, HIV-1 gp120 induces inflammasome activation in microglia *in vitro* and *in vivo*, whereas inhibiting inflammasome activation, alleviates microglia-mediated neurotoxicity, promotes neuronal regeneration, and improves cognitive function (He et al., 2020).

In summary, HIV-induced changes in mitochondrial bioenergetics, dynamics, degradation, integrity, and transport are MAM-regulated processes, implicating MAMs in HIV/HAND pathology. Noteworthy, mitochondrial fission events are key consequences of Tat-mediated toxicity in neurons (Rozzi et al., 2018; Teodorof-Diedrich and Spector, 2018), astrocytes (Ojeda et al., 2018; Priyanka et al., 2020), and microglia (Thangaraj et al., 2018; Rawat et al., 2019). Further, defective mitophagy is a crucial mechanism underlying HAND pathology. The accumulation of damaged mitochondria promotes inflammasome activation in astrocytes and microglia. Thus, the balance between mitophagy and inflammasome activation is a critical determinant of glial fate during HIV-1 toxicity (Ojeda et al., 2018; Rawat et al., 2019). As MAMs are the site for both mitophagy and inflammasome initiation, ER-mitochondrial cooperation is likely essential for negotiating these cellular outcomes. Finally, evidence of MAMs in HAND is further supported by a previous study in T cells showing that HIV-1 Vpr localizes to both the ER and mitochondria, and MAMs serve as a possible route for intracellular trafficking of Vpr (Huang et al., 2012). Notably, exposure to HIV-1 Vpr decreased MFN2 and Drp1 expression, impaired ER-mitochondrial interaction and morphology, and induced mitochondrial depolarization and deformation. Overexpressing MFN2 or Drp1 was able to prevent T cell mitochondrial depolarization and deformation. Additional studies in neural cells are needed to determine the role of MAMs in HAND. Moreover, HIV-1 Tat and Vpr are historically considered as nuclear proteins; however, Tat and Vpr toxicity on ER and mitochondrial homeostasis emphasizes the need to expand our classical understanding of host-viral interactions during HIV-1 infection.

POTENTIAL THERAPEUTIC TARGETS

Dysfunctional MAM-mediated mechanisms are hallmarks of neurodegenerative pathologies including AD, PD, ALS, and HAND. Notably, ER-mitochondrial contact and communication are critical in regulating mitochondrial function and health.

Throughout this review, we have specifically highlighted Ca^{2+} , UPR/ER stress, mitochondrial fission/fusion, mitophagy and inflammasome signaling pathways as potential targets to combat mitochondrial dysfunction in neural cells during HIV/HAND, whereas MAMs serve as the central therapeutic platform. **Table 1** summarizes the potential therapeutic targets discussed throughout this manuscript.

Coupling between the ER and mitochondria can increase in response to stress to tailor to the functional demands of the cell (Bravo-Sagua et al., 2016). However, whether increased/decreased contact contributes to cellular dysfunction or improves cell outcomes, remains largely unknown. Notably, forcing increased ER-mitochondrial contact in *Drosophila* was able to extend lifespan and improve overall motor function (Garrido-Maraver et al., 2020). As a MAM tether protein, MFN2 may serve as a potential target to manipulate ER-mitochondria contact and communication. Overexpression of MFN2 in CD4+ T cells restored mitochondrial integrity and increased cell viability against HIV-1 Vpr toxicity (Huang et al., 2012). However, the effects of MFN2 manipulation vary across cell types. For example, knockdown of MFN2 decreases MAM contact and communication in MEF (de Brito and Scorrano, 2008) but increases MAM contact and communication in an APP mutant in HEK 293 cells (Leal et al., 2016). It should be noted that increased MAM tethering following MFN2 knockdown decreased A β production and improved cellular outcome.

Manipulating MAM tethering can subsequently affect MAM-mediated mechanisms, such as ER to mitochondrial Ca^{2+} transfer. However, with these studies, it becomes difficult to delineate the primary therapeutic mechanism, tethering versus Ca^{2+} transfer. Conversely, studies that directly target MAM-mediated Ca^{2+} transfer provide a clear demonstration of the therapeutic potential of targeting these pathways. For example, in astrocytes exposed to HIV-1, blocking mitochondrial Ca^{2+} uptake by targeting MCU (Natarajaseenivasan et al., 2018), VDAC (Fatima et al., 2017), or cytosolic Ca^{2+} (Nooka and Ghorpade, 2017) can prevent astrocyte mitochondrial dysfunction and reverse astrocyte-mediated neurotoxicity. The same outcome was achieved by overexpression of mortalin/grp75 (Priyanka et al., 2020). However, this was due to a direct interaction of mortalin/grp75 with HIV-1 Tat leading to Tat degradation rather than modulating ER-mitochondrial Ca^{2+} transfer. This is an important discrepancy as mortalin/grp75 manipulation in neurons can protect neurons from oxidative cell death when repressed or increase susceptibility when overexpressed (Honrath et al., 2017). Similarly, blocking MCU or cytosolic Ca^{2+} in neurons improved neuronal survival against HIV-1 Tat toxicity (Kruman et al., 1998), while blocking ER Ca^{2+} release *via* RyR can also attenuate Tat-induced UPR induction and mitochondrial dysfunction (Norman et al., 2008). The potential therapeutic applications of targeting MCU and $\sigma 1\text{R}$ to regulate ER-mitochondrial Ca^{2+} transfer to combat neurodegenerative pathologies have also been previously reviewed (Liao et al., 2017; Weng et al., 2017).

Other potential upstream regulators of mitochondrial dysfunction underlying neuropathology are the three UPR/ER stress pathways. In fact, targeting UPR pathways

TABLE 1 | Potential therapeutic targets.

Manuscript	Model	Cell type	Target	Outcome
Garrido-Maraver et al., 2020	Drosophila	Drosophila	Ⓢ ER-mitochondrial contact	Extended Drosophila lifespan and improved overall motor function
Leal et al., 2016	APP mutant	HEK 293 cells	⊗ MFN2	Increased MAM contact and Ca ²⁺ transfer and decreased Aβ production
Huang et al., 2012	HIV Vpr expression	T cells	Ⓢ MFN2 and Drp1	Restored mitochondria integrity and morphology and increased cell viability
Kruman et al., 1998	HIV Tat exposure	Neurons	⊗ Cytosolic Ca ²⁺ and MCU	Protected neurons for HIV-1 Tat-mediated neurotoxicity
Norman et al., 2008	HIV Tat exposure	Neurons	⊗ RyR	Attenuated UPR induction and mitochondrial dysfunction
Fields et al., 2016	HIV+ brain tissues, Tg-gp120 mice, gp120 exposure	Neurons	Ⓢ Drp1	Restored mitochondrial dynamics and reduced neuroinflammation (astrogliosis) and neurodegeneration
Rozzi et al., 2018	HIV Tat exposure	Neurons	⊗ Drp1 (Indirect inhibition)	Prevented Tat-mediated effects on mitochondrial dynamics
He et al., 2020	HIV gp120 exposure; Tg-gp120 mice	Microglia	⊗ Inflammasome	Reduced neuroinflammation and neurodegeneration. Promoted neuronal regeneration and restored neurocognitive function
Nooka and Ghorpade, 2017	HIV, ART, and IL-1β exposure	Astrocytes	⊗ Cytosolic Ca ²⁺	Restored mitochondria integrity
Natarajaseenivasan et al., 2018	HIV Tat exposure	Astrocytes	⊗ MCU	Reversed metabolic switch and astrocyte-mediated neurotoxicity
Fatima et al., 2017	HIV Tat expression	Astrocytes	⊗ VDAC1	Reversed astrocyte-mediated neurotoxicity
Priyanka et al., 2020	HIV Tat expression	Astrocytes	Ⓢ Mortalin/grp75	Reversed astrocyte mitochondrial dysfunction and astrocyte-mediated neurotoxicity
Fan and He, 2016	HIV Tat exposure	Astrocytes	⊗ UPR/ER stress	Reversed astrocyte-mediated neurotoxicity and apoptotic signaling
Shah et al., 2016	HIV gp120 exposure; Tg-gp120 mice	Astrocytes	⊗ UPR/ER stress	Reversed astrocyte-mediated neurotoxicity and apoptotic signaling
Ma et al., 2016	HIV Tat exposure	HBMECs	⊗ UPR/ER stress	Restored mitochondria integrity and cell viability

⊗ inhibition/knockdown; Ⓢ overexpression/upregulation. Aβ, amyloid β; APP, amyloid precursor protein; ART, antiretroviral therapy; Ca²⁺, calcium; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; gp120, glycoprotein; grp75, glucose-regulated protein 75 kDa; HBMEC, human brain microvascular endothelial cells; HEK, human embryonic kidney; HIV-1, human immunodeficiency virus type 1; IL-1β, interleukin-1β; MFN, mitofusin; MCU, mitochondrial Ca²⁺ uniporter; RyR, ryanodine receptors; Tat, transactivator of transcription; Tg, transgenic; UPR, unfolded protein response; VDAC, voltage-dependent anion-selective channel; Vpr, viral protein R.

as potential neurodegenerative therapies are previously reviewed (Halliday and Mallucci, 2014; Remondelli and Renna, 2017; Martinez et al., 2019); however, these reports do not focus on UPR/ER stress in the context of mitochondrial dysfunction, regardless of the obvious crosstalk between these two organelles. In the context of HIV/HAND, blocking UPR/ER stress in astrocytes reverses astrocyte-mediated neurotoxicity and apoptotic signaling (Fan and He, 2016; Shah et al., 2016). Similarly, inhibiting UPR/ER stress in HBMECs restores mitochondrial integrity and increases cell viability during HIV-1 Tat toxicity (Ma et al., 2016). It is important to note that there are unique signaling pathways amongst the three arms in addition to their 'non-canonical' functions that remain ill-defined. However, given the potential regulation of the UPR/ER stress arms on MAM tethering [PERK/MFN2 (Munoz et al., 2013) and ATF6/VAPB (Gkogkas et al., 2008)], mitochondrial dynamics [PERK (Lebeau et al., 2018) and ATF6 (Bommiasamy et al., 2009)], ER-mitochondrial Ca²⁺ transfer [IRE1α (Carreras-Sureda et al., 2019) and ATF6 (Burkewitz et al., 2020)], and mitochondrial bioenergetics [IRE1α (Carreras-Sureda et al., 2019) and PERK (Balsa et al., 2019)], more research is needed to delineate their therapeutic

applications for regulating MAM/mitochondrial dysfunction in neurodegenerative pathologies. Moreover, IRE1α may also regulate mitochondrial dysfunction through inflammasome activation to promote inflammation (Bronner et al., 2015). Indeed, blocking inflammasome signaling in astrocyte-restricted HIV-1 gp120 transgenic mice not only reduced neuroinflammation and neurodegeneration but also promoted neuronal regeneration and restored neurocognitive function (He et al., 2020).

The therapeutic potential of targeting inflammasome signaling gains support when considering the delicate balance between inflammasome activation and mitophagy that is evident in astrocytes and microglia during HIV/HAND. Proceeding mitophagy, mitochondrial fission *via* Drp1 is required for removal of damaged mitochondria, which is essential for cellular survival. Overexpression of Drp1 in astrocyte-restricted HIV-1 gp120 transgenic mice was able to reverse HIV-1 gp120-induced mitochondrial elongation in neurons and reduce neuroinflammation (astrogliosis) and neurodegeneration (Fields et al., 2016). Similarly, Drp1 overexpression in CD4+ T cells expressing HIV-1 Vpr protected mitochondrial integrity and increased cell survival (Huang et al., 2012). Interestingly, cells

exposed to HIV-1 Tat increase Drp1 expression and activity favoring mitochondrial fragmentation. Rozzi et al. (2018) was able to prevent fragmentation by indirectly inhibiting Drp1 activation. Thus, while altered mitochondrial dynamics is a notable characteristic of HIV/HAND pathology, the therapeutic application may largely depend on the model/stimuli.

CONCLUDING REMARKS

Cooperation and communication between the ER and mitochondria are essential to ensure maintenance of cellular and organelle homeostasis. The significance of MAMs in different pathologies is indisputable; however, whether MAM dysfunction is a cause or consequence in these pathologies is not yet known. This review presents MAMs as pivotal platforms in neuropathology highlighting specific interplay of MAMs in AD, PD, and ALS. We then discuss the implications of MAMs in HAND for the first time. These reports emphasize Ca^{2+} , UPR and inflammasome signaling as potential targets to regulate MAM/mitochondrial dysfunction during neuropathological challenges.

Importantly, the presence and function of MAMs can differ across cell types and pathological conditions. A better understanding of the mechanisms regulating changes in MAMs in a respective cell type and/or pathology is critical to illuminate possible targets for therapeutic manipulation. For example, neurons are not directly infected by HIV-1; thus, indirect HIV-induced toxicity *via* infected glia is a key mechanism in HAND pathology. While glial cells (astrocytes, microglia, and oligodendrocytes) are essential for neural and CNS homeostasis, studies focusing on the presence and function of MAMs in glia are either severely deficient (astroglia) or non-existent (microglia and oligodendrocytes)

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highlighting the need to investigate ER-mitochondria contact and communication beyond the scope of neurons. Particularly, astrocytes provide essential metabolic and antioxidant support to neurons. Aberrant astrocyte mitochondrial function is a prominent threat to neuronal health and function. Targeting MAMs to manipulate astrocyte mitochondrial function could be a promising avenue to optimize the metabolic and antioxidant coupling between astrocytes and neurons and promote neuronal fitness against CNS pathologies. Moreover, microglia and astrocytes are the residential CNS immune cells participating in neuroinflammation, and MAMs may serve as key hinges for their activated/inflammatory status.

AUTHOR CONTRIBUTIONS

JP drafted the manuscript text and figures with guidance and supervision from I-WP and KB. All authors participated in editing or revising the article and agreed to be accountable for the content of the work.

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