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Emerging roles of mitochondria in synaptic transmission and neurodegeneration

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Mitochondria play numerous critical physiological functions in neurons including ATP production, Ca^{2+} regulation, lipid synthesis, ROS signaling, and the ability to trigger apoptosis. Recently developed technologies, including *in vivo* 2-photon imaging in awake behaving mice revealed that unlike in the peripheral nervous system (PNS), mitochondrial transport decreases strikingly along the axons of adult neurons of the central nervous system (CNS). Furthermore, the improvements of genetically-encoded biosensors have enabled precise monitoring of the spatial and temporal impact of mitochondria on Ca^{2+}, ATP and ROS homeostasis in a compartment-specific manner. Here, we discuss recent findings that begin to unravel novel physiological and pathophysiological properties of neuronal mitochondria at synapses. We also suggest new directions in the exploration of mitochondrial function in synaptic transmission, plasticity and neurodegeneration.

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Introduction

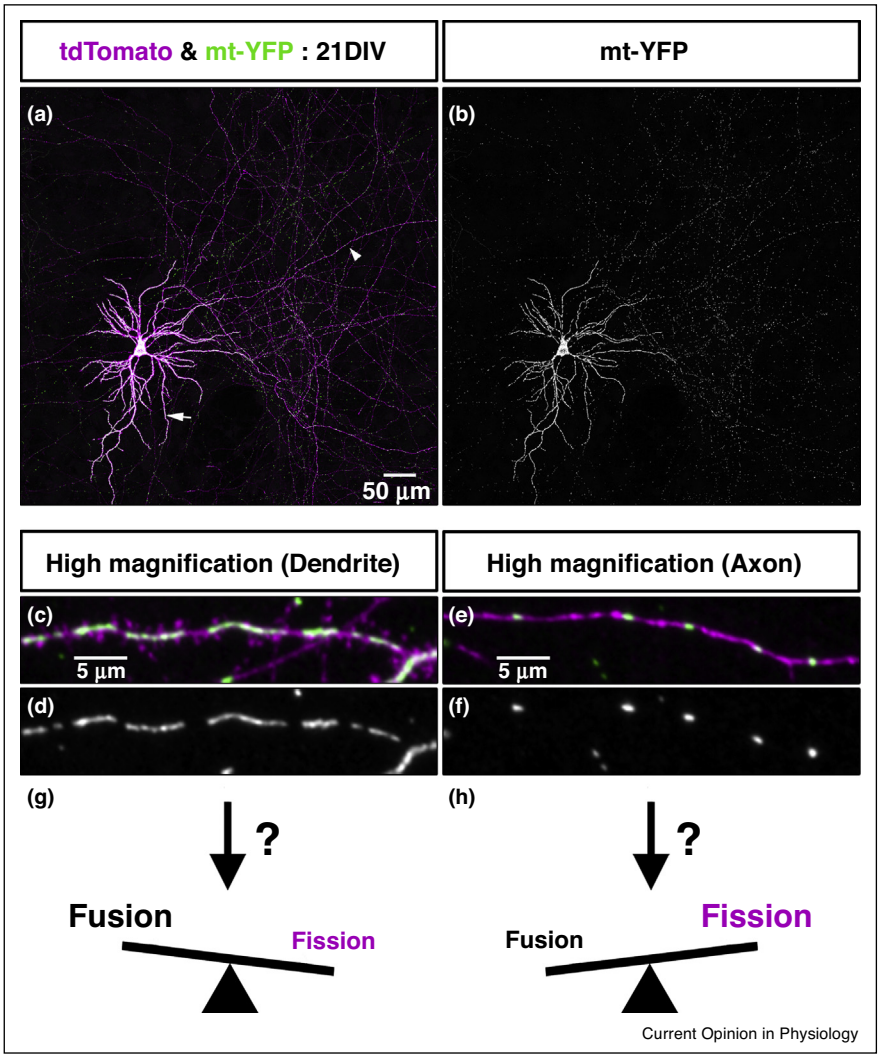
Neurons communicate with each other through specialized contacts termed synapses. Synaptic transmission between individual neurons affects neuronal development, maintenance, and brain function. The ability of mitochondria to control both cytosolic Ca^{2+} dynamics and ATP availability, both of which are crucial for proper synaptic function, makes this organelle particularly important during development and in the adult brain. Therefore, interrogating mitochondrial function in neurons is both critical for understanding normal synaptic transmission as well as in neurodegenerative diseases where synaptic function and maintenance are disrupted. We focus here on recent studies deciphering novel mechanisms in maintaining mitochondrial structure, morphology and distribution in the developing and adult CNS as well as their implications for the pathophysiological mechanisms underlying various neurodegenerative conditions.

Cell biology of mitochondria in CNS neurons

Neurons are truly unique cells whose function is largely dictated by their extreme level of compartmentalization at the cellular and molecular levels. This high degree of compartmentalization is also evident for intracellular organelles such as mitochondria which differ in their localization, morphology and function in neurons of the central nervous system (CNS). The term 'mitochondrial dynamics' encompasses a set of five distinct mitochondrial cell biological events: biogenesis, fission and fusion, trafficking, and mitophagy, a specialized form of macroautophagy [1–3].

Mitochondria display distinct morphologies and distributions in the two main compartments characterizing neurons: the axon and dendrites (Figure 1a–f). For example, in pyramidal neurons, the main excitatory neuronal subtype in the cortex, dendritic mitochondria display long and tubular shapes, forming a complex network filling ~70–80% of the dendritic arbor. In contrast, axonal mitochondria display a remarkably standard size and are small and punctate (~1 μm length), occupying <10% of axonal volume [4–6] (Figure 1a–f). In non-neuronal cell types, mitochondrial morphology is controlled mostly by fusion and fission mechanisms. Therefore, one would hypothesize that the striking differences in mitochondrial morphology between the axon and dendrites is the result of a high level of fission in the axon and high degree of fusion in dendrites. Although some studies have suggested that this is the case [7,8], the molecular mechanisms underlying compartment-specific differences in mitochondrial fission/fusion remains to be identified (Figure 1g–h). It also seems clear that these different morphologies will be accompanied by alterations in the functional abilities and output of these mitochondria, which likely include an increased or decreased ability to produce ATP or buffer calcium. How these differences in mitochondrial function

Figure 1

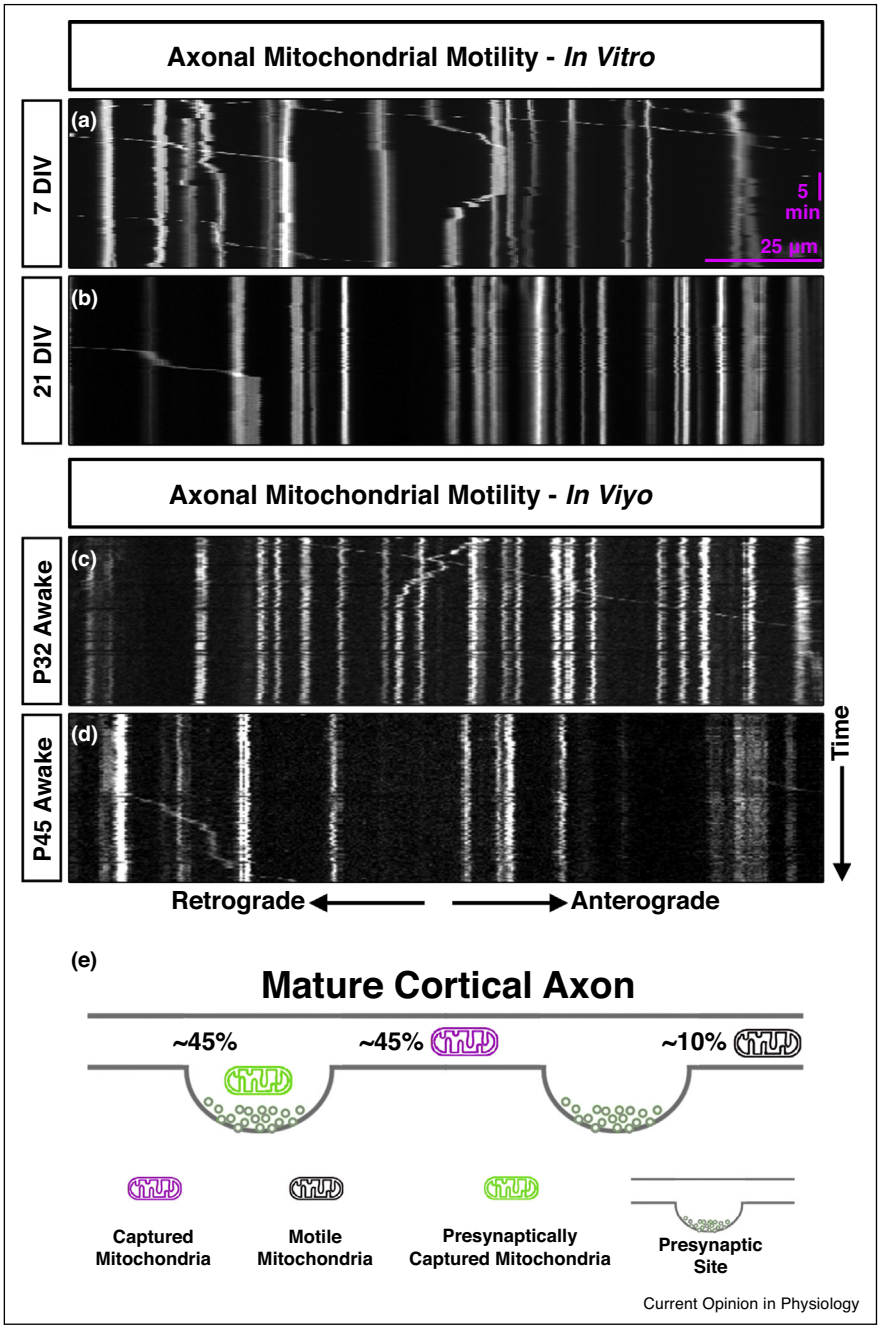


Mitochondrial morphology is compartmentalized in CNS neurons. **(a)** Single cortical neuron cultured for 21 days *in vitro* (DIV) following *ex utero* electroporation at E15.5 with plasmids encoding tdTomato (magenta) and mitochondrial targeted YFP (mt-YFP, green). **(b)** Isolated mt-YFP fluorescence from panel a. Mitochondria are long and tubular in dendrites (arrow) occupying a large fraction of the dendritic arbor, whereas in the highly branched axon (arrowhead), mitochondria are uniformly small (~1 µm length) and occupy a small fraction of the axonal volume. **(c–f)** Higher magnification images of a dendrite segment (c–d) and an axon segment (e–f) from the cortical pyramidal neuron shown in a and b. **(g)** The increased occupancy and length of mitochondria in the dendrites suggests that the balance of fission and fusion is strongly weighted toward fusion in the dendritic compartment of cortical neurons. **(h)** The much smaller size of mitochondria in the axon suggests the opposite is true in the axon where fission must be more prominent than fusion. Future work will be required to determine the cellular and molecular mechanisms that regulate this compartmentalization of mitochondria morphology in neurons. See text for details.

affect neuronal development, function or health remain completely open.

The best studied process underlying mitochondrial dynamics in neurons is their trafficking along microtubules by the microtubule-based motors kinesin and dynein [9,10]. In axons, microtubules display a unique orientation with their polymerizing plus-end oriented away from the cell body [11]. Using a number of different methods, many studies have revealed that there are at least two pools of mitochondria: a motile and an immobile (or stationary) pool [12•,10,13]. The current consensus in developing neurons is that each pool comprises around 50% of the mitochondria (Figure 2a). However, recent work from multiple labs using models from flies to mice, both *in vitro* and *in vivo*, revealed that mitochondrial trafficking decreases significantly with neuronal maturation [14•,12•,15•,16]. For instance, in axons of adult layer 2/3 cortical pyramidal neurons, the ratio of stationary to motile mitochondria is approximately of 9:1 both *in vitro*

Figure 2



Mitochondrial trafficking decreases with axonal development as mitochondria become captured at specific points along the axon. **(a)** Kymograph of mitochondrial movement (visualized via time lapse microscopy of YFP-labeled mitochondria at 0.1 frame per second (fps) in the axon of a 7DIV cortical neuron demonstrating a profile of ~50% motile and ~50% stationary pools of mitochondria. **(b)** Kymograph of mitochondrial movement in the axon of a 21DIV cortical neuron showing ~95% captured mitochondria and an ~5% motile pool. **(c)** Kymograph of mitochondrial movement in the distal axon of a layer 2/3 cortical neuron in a (P)ostnatal day 32 awake behaving mouse. **(d)** Kymograph of mitochondrial movement in the distal axon of a layer 2/3 cortical neuron in a P45 awake behaving mouse. c and d illustrate that ~90% of mitochondria in mature axons *in vivo* are captured at specific points along the axon. **(e)** Schematic representation of mitochondrial localization along mature cortical axons *in vitro* and *in vivo*. Future work will be necessary to identify the different locations of mitochondrial capture as well as the molecular mechanisms that regulate these long term capture events.

and *in vivo* (Figure 2b–d). At least two sites of mitochondrial capture have been identified in developing axons: '*en passant*' presynaptic synapses and branch points [17,18]. The axon of cortical pyramidal neurons form thousands of '*en passant*' synapses which are synapses made along the entire length of the axon as opposed to the axon 'terminal' of specialized neuronal subtypes, such as motor neurons forming only synapses at the end of their axon that is the neuromuscular junction. In these cortical axons, like many other central nervous system neuron subtypes, >90% of mitochondria appear immobile for long periods of time (~45% of axonal mitochondria are captured at presynaptic sites while 45% are associated with sites of currently unknown relevance [17,13]). These observations raise a number of important questions currently being addressed by the field: What are the molecular mechanisms underlying the long-term 'capture' of mitochondria? What are the specific locations where mitochondria are captured along axons? Is mitochondrial function altered upon capture at different sites? The first of these questions has already been partially answered by several studies suggesting that the first step in arresting mitochondria trafficking along the axon depends on Ca^{2+}-dependent release from microtubules through the combined functions of Miro/Milton and/or syntaphilin [19–21] which are key adaptors/modifiers of the microtubule motors, kinesins and dyneins. However, we propose that other currently unknown mechanisms also likely exist to mediate a more permanent 'anchoring' of mitochondria at presynaptic boutons or at other locations along the axon.

Synaptic functions of mitochondria

The ability of mitochondria to generate ATP and uptake Ca^{2+}, both of which affect presynaptic release properties, has been extensively studied. Neurotransmitter-containing synaptic vesicle (SV) exocytosis is triggered by Ca^{2+} entry through voltage-gated Ca^{2+} channels (VGCC) upon action potential invasion of the presynaptic bouton, where synapses occur in axons. This Ca^{2+}-dependent exocytosis of neurotransmitter vesicles is coupled to endocytosis in order to maintain SV pool size under physiological conditions. Therefore, regulating presynaptic Ca^{2+} homeostasis and controlling SV pool size are critical for proper synaptic transmission.

Presynaptic cytoplasmic Ca^{2+} can be cleared by multiple, potentially complementary mechanisms: first, through plasma membrane Ca^{2+}-ATPase (PMCA) to the extracellular space, second, through smooth endoplasmic reticulum Ca^{2+}-ATPase (SERCA) to the endoplasmic reticulum, or third, through mitochondrial Ca^{2+} uniporter (MCU) to the mitochondrial matrix [22–26]. The relative contribution of each of these mechanisms is unclear and might actually be synapse-specific [27]. Mitochondrial contribution to presynaptic Ca^{2+} buffering has been suggested from studies including large synaptic terminals such as *Drosophila* neuromuscular junction (NMJ), mammalian NMJ, and the calyx of Held [27]. Moreover, recent studies using genetically encoded sensors probing Ca^{2+} dynamics and SV release demonstrated critical roles for mitochondria at individual presynaptic release sites of CNS axons making thousands of small (~1micron length) *en passant* boutons [28•,29•30•]. As mentioned above, approximately 50% of presynaptic *en passant* boutons are associated with mitochondria, and our work as well as others, recently showed that mitochondria-free boutons of cortical or hippocampal neurons accumulate more Ca^{2+} upon repetitive (5–20 action potentials (AP) at 10 Hz) stimulation, thereby triggering progressively more SV release during train of AP [29•,30•]. Furthermore, reduced MCU-dependent presynaptic mitochondrial Ca^{2+} uptake caused increased cytoplasmic presynaptic Ca^{2+} accumulation and impaired short-term synaptic plasticity and asynchronous release [29•]. Variation in levels of neuronal activity level can scale (up or down) neuronal excitability in order to bring neural network activity within a certain range, and mitochondrial occupancy at individual presynaptic boutons can play an important role in this form of homeostatic rescaling [30•]. Paradoxically, with the notion that presynaptic mitochondrial function is primarily to generate ATP [31], these recent results suggest that the presence of mitochondria corresponds to boutons releasing at lower probability compared to boutons devoid of mitochondria along the same axon [29•,30•].

Historically, ATP has been proposed to play critical roles presynaptically, such as SV endocytosis and neurotransmitter re-uptake in presynaptic vesicles. Therefore, mitochondrial ATP generation has been suggested to maintain SV pool size. Moreover, a recently developed ATP sensor directly showed activity-driven ATP generation at presynaptic sites [31]. However, in these studies, ATP is monitored during presynaptic neurotransmitter release evoked by high, non-physiological regimes of action potential stimulations (600AP i.e. 60 s stimulation at 10 Hz). Moreover, even in these extreme conditions (never encountered by cortical or hippocampal pyramidal neurons *in vivo*), blocking either glycolysis or the mitochondrial ATP synthase results in only modest changes in presynaptic ATP concentrations. Even more intriguing, as mentioned above, in axons of cortical pyramidal neurons, only 50% of presynaptic release sites are associated with a mitochondria [12•]. In fact, a recent study compared changes in ATP concentration (using a genetically-encoded ATP sensor) in presynaptic boutons with or without mitochondria and found no difference, even during strong stimulation of neurotransmitter release (600AP) [32]. Collectively, these results suggest that presynaptic mitochondria in adult mammalian CNS axons are likely not the major source of ATP and that glycolysis or other means of generating ATP provide a sizeable proportion of the ATP required for synaptic activity. Interestingly, glycolysis-related proteins are enriched at

presynaptic sites upon synaptic stimulation, suggesting that glycolysis may supply enough ATP to sustain physiological levels of activity in axons [33•,34••].

In dendrites of cortical pyramidal neurons, long and tubular mitochondria occupy a significant volume of the dendritic arbor (~70%), but are restricted to the dendritic shaft and largely excluded from spines [6,35•] (Figure 1). Postsynaptic/dendritic Ca^{2+} dynamics also plays critical roles including synaptic integration and gene expression regulation. In dendrites, extracellular and endoplasmic reticulum (ER)-stored Ca^{2+} are the main sources of dendritic Ca^{2+}. However, in this context, the role of mitochondria in postsynaptic function is largely unknown despite the large volume they occupy. Recent 3D-serial electron microscopy (3D-SEM) reconstruction data revealed that dendritic ER and mitochondria make many contacts along the dendrite [35•]. Furthermore, our lab recently identified that a significant fraction of synaptically-induced Ca^{2+} released from the ER is directly transferred to mitochondria at these ER-mitochondria contact sites. This was uncovered through the identification of PDZD8, a novel ER-mitochondria tethering protein in multiple mammalian cell types [36••] which represents a functional paralog of the yeast protein Mmm1, one of the four proteins composing the ERMES ER-mitochondria tethering complex in this cell type. Interestingly, in dendrites of PDZD8-deficient cortical pyramidal neurons, a significantly higher fraction of synaptically-evoked Ca^{2+} release from the ER leaks to the cytosol, therefore increasing local dendritic Ca^{2+} concentration. These results suggest that the distribution and extent of ER-mitochondria contacts in neuronal dendrites might control the spatial and temporal aspects of dendritic Ca^{2+} dynamics and thereby might underlie dendritic branch-specific properties of synaptic integration and/or plasticity.

In addition, 3D-serial EM reconstructions also visualized the structure of axonal ER and mitochondria, where they also form large contacts [35•]. Our own reconstructions from serial EM of layer 4/5 mouse cortex demonstrate that presynaptic mitochondria form extended contacts with the axonal ER (Figure 3a and c–d). Interestingly, in dendrites, ER-released Ca^{2+} can be conveyed to mitochondria through their contact sites, as mentioned above; however this has not been observed yet at presynaptic boutons of CNS axons. Surprisingly, a novel genetically-encoded ER Ca^{2+} sensor demonstrates that axonal ER can effectively uptake Ca^{2+} without any detectable release of Ca^{2+} at presynaptic boutons of cortical axons *in vitro* [37]. Therefore, understanding how mitochondria-ER contacts regulate presynaptic function will be pivotal for the field.

Disruption of mitochondrial dynamics and neurodegeneration

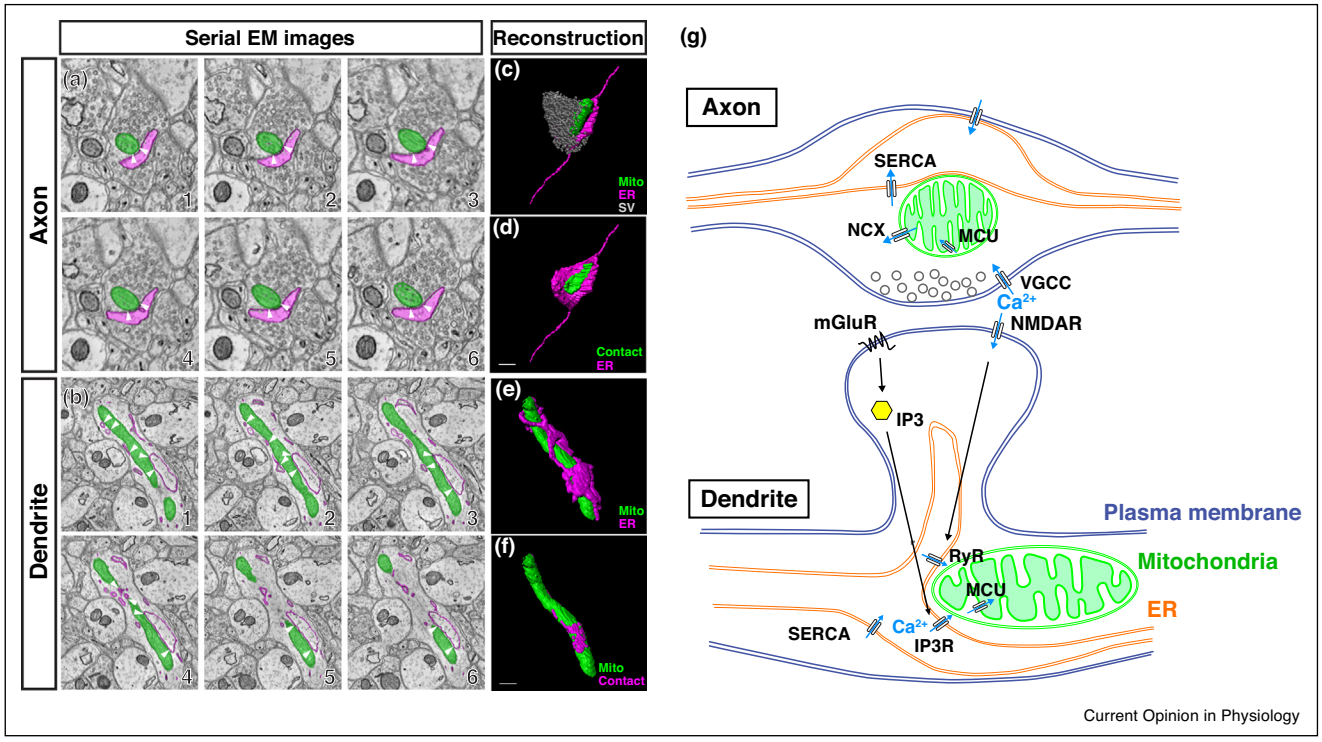
Several studies have highlighted the frequent role of mitochondria in the pathogenesis of a wide range of neurodegenerative diseases (ND). Due to the limitation of space, we focus this portion of our review on prototypical examples of ND as listed in Table 1. Below, we explore some recent reports demonstrating disruptions in mitochondrial homeostasis, motility, and dynamics observed upon neurodegeneration.

Mitochondria quality control through fission, fusion, and mitophagy

In non-neuronal cells, mitochondrial homeostasis is tightly regulated by a dynamic balance of fission, fusion and mitochondrial autophagy (mitophagy). Changes in mitochondrial morphology have been implicated in Alzheimer's disease (AD) through observations of altered mitochondrial fission and fusion protein levels in AD patient brains. Corroborating some of the postmortem analysis of human patient samples, primary neuronal culture *in vitro* showed shorter mitochondria upon exposure to amyloid-β derived diffusible ligand (ADDL), which appears critical for synapse elimination during early stages of the disease progression [38]. More recent studies using 3D-SEM reconstructions showed that various AD mouse models display a 'mitochondria-on-a-string' (MOAS) phenotype in neurites from CA1 where reduced mitochondrial matrix volume is observed together with continuous but constricted outer mitochondrial membrane (OMM). Although the authors do not distinguish the specific cell type they are evaluating, they hypothesized that the MOAS phenotype that is observed in AD mouse models occur due to potentially disrupted function of Drp1, ultimately resulting in an incomplete fission pattern [39•]. In line with morphological changes, increased mitochondrial stress response, including increased mitophagy genes, have recently been reported across — species from *Caenorhabditis elegans* to humans, in response to Aβ accumulation [40•]. Currently, the exact molecular mechanisms underlying these changes in mitochondrial morphology and mitophagy dynamics are unclear. Whether these changes play a causal role in the neuropathology or represent an attempt for neurons to cope with a form of cellular stress induced by Aβ is still unclear, but disruption of mitochondrial homeostasis is becoming a common phenotype in various models of AD [41,38,39•].

Multiple lines of evidence suggesting disrupted mitochondrial homeostasis in Parkinson's disease (PD) have emerged from studying mutations of genes linked to familial forms of PD including Parkin, a E3 ubiquitin ligase, and PINK1 kinase. These two genes are involved in mitophagy, implicating their mutations in the disruption of mitochondrial integrity [42••,41]. However, how these two proteins directly influence mitochondrial morphology and function is still under debate, as Parkin has many downstream effectors, and because many of the functions of Pink1/Parkin have been studied under non-physiological conditions [41]. Another interesting

Figure 3



Contacts between the ER and mitochondria in the dendrites and axons. **(a, b)** Serial electron microscopy (EM) images of axon and dendritic segment of pyramidal neurons in layer 4/5 of the primary somatosensory area of mouse neocortex (publicly available data — [6]; https://neurodata.io/data/kasthuri15). Individual mitochondria and the ER network located in segments of the axon (a) and dendrite (b) are highlighted in green and magenta, respectively. Arrowheads indicate ER-mitochondria contact sites. **(c–f)** 3D reconstructions of the serial EM images shown in a (c, d) and b (e, f). The ER is made of a thin, tubular structure along the axon shaft that systematically bulges specifically at the presynaptic sites (c, d), while having a complex network-like structure in dendrites (e, f). There are extensive contacts between the ER and mitochondria both in the axon and dendrites (d, f). (c) Synaptic vesicles, grey; mitochondria, green; ER, magenta; (d) ER-mitochondria contact site, green; ER, magenta; (e) mitochondria, green; ER, magenta; (f) mitochondria, green; ER-mitochondria contact site, magenta. Scale bar; 300 nm. **(g)** A diagram showing ER and mitochondrial-dependent regulation of Ca^{2+} dynamics in axons and dendrites (modified from [36••]). Synaptic stimulation induces Ca^{2+} entry through VGCC (voltage-gated Ca^{2+} channel) at the presynaptic sites. Ca^{2+} is partially cleared by MCU-dependent mitochondrial Ca^{2+} uptake. In dendrites, Ca^{2+} entry through ligand-gated ion channels and VGCC can induce Ca^{2+} release from RyR (ryanodine receptor). In addition, IP3 (inositol 1,4,5-trisphosphate) generated downstream of a metabotropic glutamate receptors (mGluR) activation induces Ca^{2+} release from the ER through IP3 receptors (IP3R). Mitochondria buffers a significant fraction of Ca^{2+} released from the ER, which at the expense of the fraction of Ca^{2+} ending in the cytoplasm.

autosomal recessive mutation in a familial form of PD affects the gene encoding DJ1, which localizes to mitochondria. However, one of the biggest caveats in studying these genes is that PINK1, Parkin, and DJ1 knockout mice do not display any dramatic phenotypes in neurons, bring into question the importance of mitochondrial quality control in the disease pathogenesis [43]. However, a recent study emphasized how DJ1 mutations in human iPSCs differentiated into dopaminergic neurons (DA) influences mitochondrial function. Compared to mouse iPSCs where the same mutations show little phenotypic effects, human iPSCs showed elevated mitochondrial oxidative stress. How the elevated mitochondrial oxidative stress can directly influence their morphology is unclear, but this is one of first papers highlighting the unique susceptibility PD mutations might have on human, but not mouse, DA neurons [44••]. Lastly, PD associated mutation of VPS35, a membrane protein found on the recycling retromer complex, has been proposed to regulate mitochondrial morphology through disruption of Drp1 recycling [45]. Further study is needed to test if these changes in mitochondrial structure and function have a causal role in Parkinson's disease progression.

Structural evidence of altered and aggregated mitochondria has been observed in motor neurons of ALS patients [46]. Interestingly, many of the genes mutated in the familial forms of ALS, such as optineurin, p62, and TBK1, regulate mitophagy. Several familial ALS mutations also disrupt ATP generation, ROS production, and Ca^{2+} buffering in part by altered interaction with the ER.

The loss of ER-mitochondria communication is an emerging mechanism for disrupted Ca^{2+} due to mutations of SOD1, TDP43, and FUS-related ALS, where reduced Ca^{2+} uptake in mitochondria from the ER leads to increased cytosolic Ca^{2+} [46]. However, the molecular players involved in this remain unclear, especially because novel ER-mitochondrial proteins are still being discovered [36••]. A recent study also suggested that mutation on TDP43 results in increased localization of the protein to mitochondria, and that this ALS-associated mutation allows TDP43 to bind to mtDNA to disrupt its transcription, ultimately leading to mitochondrial fragmentation and dysfunction [47•]. Despite the different consequences of these mutations, disrupted mitochondrial homeostasis is emerging as a common feature of ALS.

Table 1

Proteins associated with major neurodegenerative diseases and their involvement with mitochondrial disruption

Disease	Genetic cause	Description of gene	Potential consequences of mutations on mitochondrial function	References
Alzheimer's disease (AD)	APP	Trans-membrane protein that give rise to Aβ peptides Oligomeric form of Aβ are thought to have a causal role in AD and aggregate to form senile plaques	Altered levels of mitochondrial fission and fusion proteins that ultimately leads to abnormal mitochondrial distribution Disrupted mitochondrial trafficking Reduced mitochondrial membrane potential and ATP levels Increase of mitochondrial on a string (MOAS) phenotype Increased apoptotic response and free radical production	Reviewed by Schon and Przedborski [41] Wang *et al*. [38] Lin and Beal [51] Zhang *et al*. [39•]
	PS1 & 2	Component of γ secretase that cleaves APP to produce Aβ peptides	Altered mitochondrial motility and mitochondrial activity that ultimately leads to changes in brain energetics	Zhang *et al*. [39•]
	TREM2	Surface receptor required for microglial response	Lowered mitochondrial mass and activated caspase in microglia thought to disrupt microglial function to degrade aggregates or proteinopathy	Ulland *et al*. [53]
Parkinson's disease (PD)	α-Synuclein	Function unclear; thought to be involved in membrane remodeling at nerve terminals Major component of Lewy bodies	Disrupted mitochondrial trafficking Fragmented mitochondria	Reviewed by Schon and Przedborski [41]
	Parkin	Cytosolic E3 ubiquitin ligase localized to mitochondria Novel function shown to inhibit formation of mitochondrial derived vesicles (MDV) involved in mitochondrial antigen presentation (MitoAP)	Altered mitochondrial morphology and mitophagy Increased oxidative stress Increased MDV formation and activated MitoAP thought to elicit cytotoxic response	Reviewed by Schon and Przedborski [41] Matheoud *et al*. [42••]
	PINK1	Kinase localized to mitochondria Novel function to inhibit formation of MDV involved in MitoAP	Altered mitochondrial morphology and mitophagy Increased MDV and activated MitoAP thought to elicit cytotoxic response	Reviewed by Schon and Przedborski [41] Matheoud *et al*. [42••]
	DJ-1	Hypothesized to be involved in regulating oxidative stress & protecting against cell death	Increased mitochondrial oxidative stress Decreased oxygen consumption rate by mitochondria	Burbulla *et al*. [44••]
	LRRK2	Kinase with unclear function Recently proposed to remove Miro1 in stalled mitochondria	Delayed mitophagy in part by stabilizing Miro1 on damaged mitochondria and prolonging active transport Altered mitochondrial morphology is controversial	Hsieh *et al*. [50]
	VPS35	Membrane protein part of recycling retromer complex	Fragmented mitochondria Reduce levels of ATP and membrane potential Impaired bioenergetics	Wang *et al*. [45,47•]

Table 1 (*Continued*)

Disease	Genetic cause	Description of gene	Potential consequences of mutations on mitochondrial function	References
Amyotrophic lateral sclerosis (ALS)	SOD1	Cu/Zn superoxide dismutase; antioxidative function	Disrupted mitochondrial trafficking and energy metabolism Reduced calcium-loading capacity in mitochondria Increased cytochrome c release and apoptosis Clogged protein importation machinery and reduced ETC activity Altered ROS production (but note, it's thought that there is toxic forms of mutants that drive the phenotype, and NOT the reduction of its dismutase activity)	Reviewed by Schon and Przedborski [41] Lin and Beal [51] Smith *et al*. [46] Taylor *et al*. [55]
	ALS2	Guanine nucleotide exchange factor (GEF)	Decreased mitophagy causing recessive juvenile form of ALS	Smith *et al*. [46]
	FUS	RNA-binding protein	Disrupted mitochondrial function including decreased ATP generation, loss of mitochondrial calcium uptake, increased ROS production Disrupted mitochondrial trafficking, mitochondrial morphology, and mitophagy Disrupted ER-mitochondrial contacts	Smith *et al*. [46]
	VAPB	Function unclear but implicated in vesicle trafficking and calcium homeostasis	Impaired mitochondrial calcium uptake Disrupted mitochondrial trafficking Disrupted ER-mitochondria contacts	Smith *et al*. [46]
	TARDBP	RNA-binding protein	Reduced mitochondrial length and mal-distribution of mitochondria in cell body and reduced mitochondrial levels in distal motor axon terminals Altered complex I disassembly Impaired ER-mito communication that leads to calcium mishandling	Reviewed by Schon and Przedborski [41] Smith *et al*. [46] Wang *et al*. [45,47•]
	OPTN	LC3 adaptor involved in mitophagy	Disrupted recruitment to the mitochondria and therefore disrupted mitophagy	Reviewed by Schon and Przedborski [41] Smith *et al*. [46]
	SQSTM1	LC3 adaptor also involved in mitophagy	Disrupted interaction with LC3 and therefore disrupted mitophagy Reduced mitochondrial membrane potential	Smith *et al*. [46]
	TBK1	Kinase that can phosphorylate OPTN and SQSTM1 to promote LC3 binding	Impaired clearance of LC3 labeled autophagic cargoes including mitochondria	Smith *et al*. [46]
	VCP	Type II AAA+ ATPase Involved in dislodging damaged ubiquitinated proteins from complexes for proteosomal dependent degradation, essential for mitophagy	Disrupted mitochondrial trafficking Increased mitochondrial uncoupling and reduced ATP production Reduced mitophagy	Reviewed by Schon and Przedborski [41] Smith *et al*. [46]
	SIGMA-1 Receptor (σ1R)	Localizes to ER-mitochondria contacts and modulates IP3 receptor-dependent Ca^{2+} release from ER	Disrupted mitochondrial trafficking Disrupted ER-mitochondrial contacts and dysregulated calcium homeostasis	Smith *et al*. [46]
	C9orf72	Unclear function hypothesized to be guanine nucleotide exchange factor	Altered mitochondrial morphology and membrane potential Increased oxidative stress (increased mtROS production)	Smith *et al*. [46] Lopez-Gonzales *et al*. [54]
	CHCHD10	Mitochondrial protein localized between inner mitochondrial membrane and outer mitochondrial membrane	Disrupted of mitochondrial cristae morphology Reduced oxidative phosphorylation	Smith *et al*. [46]

Table 1 (*Continued*)

Disease	Genetic cause	Description of gene	Potential consequences of mutations on mitochondrial function	References
Huntington's disease (HD)	Huntingtin	Very large cytoplasmic protein playing pleiotropic functions in neurons Regulates trafficking of mitochondria and other cargoes such as synaptic vesicles (can bind with Huntington-associated protein, which interact with mitochondria and both kinesin and dynein/dynactin	Impaired mitochondria trafficking Altered mitochondrial fission/fusion protein expression Fragmented mitochondria and altered mitochondrial dynamics Disrupted mitochondrial respiration	Reviewed by Schon and Przedborski [41] and Saudou and Humbert [52] Lin and Beal [51]

Mitochondrial trafficking and distribution in neurodegenerative diseases

Mitochondrial trafficking allows the specific distribution of mitochondria in subcellular compartments, permitting them to carry out localized functions. This is particularly important in neurons due to their polarized morphology. Disrupted mitochondrial trafficking was hypothesized in AD when patient samples showed axonal swelling filled with mitochondria as well as other vesicles, vacuoles, and multi-vesicular bodies (MVB). Subsequent studies using mouse models overexpressing familial AD linked mutations also suggested disrupted mitochondrial trafficking in relatively immature cortical axons *in vitro* [41,48]. However, recent data demonstrated that mitochondrial trafficking in mature, adult axons of cortical pyramidal neurons both *in vitro* and *in vivo* is dramatically lower than previously reported [12•,15•]. Therefore, these previous results obtained *in vitro* will need to be re-evaluated using either mature cortical neuron cultures (>21DIV) or ideally using *in vivo* 2-photon imaging approaches in adult or aging AD mouse models.

Although the direct consequence of mutations linked with PD on mitochondrial trafficking is still unclear, many studies suggest disrupted mitochondrial motility in axons. PINK1 has been shown to interact with Miro directly on depolarized mitochondria which ultimately leads to Parkin dependent degradation of Miro, potentially as a mechanism to stall and isolate damaged mitochondria [49]. Other PD-associated genes such as Parkin, α-synuclein, and leucine-rich repeat kinase 2 (LRRK2) have been linked to alteration of microtubule (MT) dynamics, suggesting that MT-dependent trafficking of several axonal cargoes such mitochondria, could be disrupted by these mutations [41]. Interestingly, recent studies suggest that some mutations associated with neurodegeneration influence the expression level of MT adaptors. Mutations of LRRK2, for example, delay the degradation of Miro from the outer mitochondria membrane under stress. This not only alters mitochondrial motility, but also slows down the recruitment of the mitophagic players for proper degradation of damaged mitochondria [50]. The ultimate effect of LRRK2 mutations on mitochondrial morphology/function in mammalian CNS neurons is still unclear, but the authors propose that the function of LRRK2 to degrade Miro1 is Pink1/Parkin-independent [50].

Changes in mitochondrial dynamics have also been observed in animal mouse models and patients samples from Huntington disease (HD) patients. Although the exact function of Huntingtin (Htt) is unclear in this context as it is a large pleitropic adaptor protein, studies on HD-associated mutations of Htt suggested altered mitochondrial dynamics, especially since Htt can interact with mitochondria and regulators of mitochondrial trafficking [51,52].

Emerging views and concluding remarks

It is important to note that many studies have a neurocentric view in determining how mitochondria disruption influences neurons in the brain during neurodegeneration. However, the field is beginning to recognize the role of other cell types in neurodegenerative diseases. In the case of AD, a recent gene variant associated with late-onset AD, TREM2, has been identified to function as an immune receptor on microglia. Mutations of this gene lead to lowered mitochondrial mass and decreased metabolites from the TCA and glycolysis pathways in microglia, and are thought to result in global microglial dysfunction correlating with the progression of AD [53]. The role of immune response in PD has also been raised. Interestingly, a novel function of Parkin and PINK1 include inhibiting the dynamics of mitochondrial-derived vesicles (MDVs). These MDVs can be exported to present antigens on the cell surface to initiate autoimmune responses that ultimately lead to neuronal cell death [42••]. Mutations of Parkin and PINK1 are hypothesized to increase MDV dependent antigen presentation, eliciting a neuroinflammatory response. Although the above studies highlight a common mitochondrial dysfunction in many ND, it is often unclear whether mitochondria have a causal role in disease progression or if their dysfunction is merely a consequence due to other forms of cellular toxicities and various forms of stress responses.

Despite the tremendous efforts to treat these diseases, many of the available treatments show mild results at best, suggesting a need for novel approaches. Because mitochondrial dysfunction and or remodeling has been reported in multiple forms of ND, enhancing mitochondrial function or maintaining their structural integrity has been proposed to delay the onset of ND [41]. Before diving into this endeavor, it will be critical to understand and dissect the key mechanisms behind the observed mitochondrial dysfunction in hopes of identifying new potential therapeutic approaches for neurodegenerative diseases.

Conflict of interest

None declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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