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Mitochondrial heterogeneity and homeostasis through the lens of a neuron

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Abstract

Mitochondria are vital organelles with distinct morphological features and functional properties. The dynamic network of mitochondria undergoes structural and functional adaptations in response to cell-type-specific metabolic demands. Even within the same cell, mitochondria can display wide diversity and separate into functionally distinct subpopulations. Mitochondrial heterogeneity supports unique subcellular functions and is crucial to polarized cells, such as neurons. The spatiotemporal metabolic burden within the complex shape of a neuron requires precisely localized mitochondria. By travelling great lengths throughout neurons and experiencing bouts of immobility, mitochondria meet distant local fuel demands. Understanding mitochondrial heterogeneity and homeostasis mechanisms in neurons provides a framework to probe their significance to many other cell types. Here, we put forth an outline of the multifaceted role of mitochondria in regulating neuronal physiology and cellular functions more broadly.

Mitochondria orchestrate diverse metabolic and stress-response pathways in cells. The function of mitochondria is not limited to adenosine triphosphate (ATP) synthesis through oxidative phosphorylation. They also play a central role in Ca^{2+} storage, the initiation of cell death, and the synthesis of biomolecules, including haeme compounds[1], neurotransmitters[2], and hormones[3]. Therefore, it is not surprising that mitochondrial dysfunction is associated

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Author contributions

Both authors conceived the idea and wrote the paper.

Competing interests

X. W. is a co-founder, adviser, and shareholder of AcureX Therapeutics, and a shareholder of Mitokinin Inc. Both companies develop therapeutics that target mitochondria for neurodegenerative diseases. G. P. declares no competing interests.

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with a spectrum of diseases, ranging from inborn metabolic errors to age-dependent neurodegeneration, among others.

Originally perceived as singular and stationary structures, mitochondria form highly dynamic networks in many cell types[4]. Although mitochondrial organization and spatiotemporal energy levels have mostly been studied in large polarized cells such as neurons (which are up to a metre long in humans)[5,6], it has long been assumed that, in a typical cell (ranging from 25–75 μm), the intracellular functions of mitochondria are homogeneous. However, recently it has been demonstrated that the positioning of mitochondria regulates local energy gradients and heterogenous metabolic functions, even in smaller cells[7,8].

Mitochondria exhibit remarkable morphological and functional plasticity in a neuron, which allows them to meet local metabolic demands. Neurons are composed of exceptionally polarized long axons and dendritic processes. This complex neuronal geometry allows each neuron to contain anywhere from hundreds to hundreds of thousands of synapses (Box 1). The spatiotemporally distinctive energy landscape shapes many functional aspects of a neuron, from action-potential firing to synaptic-vesicle recycling at the synapses. The heterogeneity of mitochondria makes them well suited to unique subcellular neuronal functions. Considering that cellular polarity is an essential feature within a tissue, mechanisms identified in neurons for fine-tuning local mitochondria and regulating their diversity could be fundamental to many cell types. Here, we will discuss cellular mitochondrial heterogeneity and homeostasis mechanisms, with a special focus on mitochondria in neurons. We will explore how neurons control mitochondrial properties to maximize their functional output in specialized subcellular compartments, illuminate the pleiotropic role of mitochondria in neurological diseases, and present our forwards-looking view on the field for mitochondrial biologists and neuroscientists.

Matching mitochondrial functions to cellular needs

Mitochondria have the capacity to maintain functionally, metabolically, and morphologically distinct subpopulations, largely determined by their motility and fission-and-fusion rate[9]. Mitochondrial distribution in cells is achieved by motor and adapter proteins that move mitochondria along cytoskeletal tracks. In many cells, such as neurons, fibroblasts, and pancreatic cells, mitochondria undergo directional transport on microtubules or actin filaments[4]. For example, in neuronal axons, mitochondria move along microtubules from the cell body to reach the distal synapses, with instant energy requirements (Fig. 1a)[10–14]. In contrast, in other cell types, such as cardiomyocytes and skeletal muscle cells, mitochondria form an organized and stable network (Fig. 1b), aligning with myofibrils to provide an extended local energy reserve for muscle contraction[4]. In some cells, such as fibroblasts and lymphocytes, mitochondrial distribution is relatively even (Fig. 1c,d); however, their motility and morphology can shift during cell activation or metabolic adaptation[15,16].

The mitochondrial proteome displays a great level of heterogeneity across heart, fat, liver, pancreas, muscle, and brain tissues, which implies profound functional consequences[17]. In the context of the brain, where cellular diversity is extremely complex, the emerging

question is how specific cell classes regulate mitochondrial functions on the basis of their unique metabolic needs. Neuronal mitochondria have distinct protein composition, lipid metabolism, Ca^{2+} buffering properties, and inter-organellar interactions[18,19]. Although little is known about the precise role of cell-type-specific mitochondrial heterogeneity in the brain, preservation of mitochondrial functions in neurons under certain circumstances may require neuron-supporting cells, such as astrocytes and oligodendrocytes. For example, during intense synaptic transmission or glucose deprivation, mitochondria in glia may play a supportive role for neuronal metabolism[20,21]. Overall, metabolic coordination between neurons and other cell types is critical for sustaining brain energy homeostasis.

In a neuron, mitochondria form an extensively connected and dynamic network in the somatodendritic area and are mostly in a singular state in the axon (Fig. 1a). Mitochondria clustered at the synapses constitute a discrete pool from their non-synaptic counterparts, exhibiting distinguishable morphological[22,23], proteomic[22,24], enzymatic[22,25], and Ca^{2+} handling characteristics[26], and increased vulnerability to oxidative damage[24,27]. These unique features are likely determined by the activity in the synaptic microenvironment. Synaptic activity results in high Ca^{2+} influxes and demands instant ATP supply. The synaptic mitochondrial pool may have adapted its ability to buffer Ca^{2+} and oxidants to better support neuronal functions. In other cells, such as adipocytes and striated muscles, lipid-droplet-associated mitochondria (LDM) are physically segregated from cytoplasmic mitochondria (Fig. 1e) and display distinct proteomic and metabolic properties[9]. For example, in brown adipose tissue, LDM have a lessened ability to oxidize fatty acids. These mitochondria are dissociated from lipid droplets upon cold exposure when fatty acids are oxidized to generate heat, indicating a specialized role for LDM in lipid storage rather than oxidation[9]. Understanding the significance of mitochondrial heterogeneity and its contribution to cellular energy homeostasis will not only help us uncover the bioenergetic regulation of organismal fitness, but also provide clues to disease mechanisms. We will next discuss lessons learnt from neurons, because of their unique reliance on mitochondrial diversity.

The coupling between brain energy metabolism and neuronal activity

Neurons consume ~15% of the body's resting energy to sustain action potential, neurotransmitter release, cytoskeletal dynamics, and gene expression[11]. Despite the large energy demands, neurons do not store energy, but rather instantly and locally synthesize it in the form of ATP[12]. Therefore, it is not surprising that metabolic insults, including acute episodes of ischaemia, mitochondrial poisons, or hypoglycaemia, cause a rapid decline in nervous-system function. Even minor disruptions of neuronal energy homeostasis, which sometimes occur in neurodegenerative diseases, can restrict the information-processing power of the brain.

The central nervous system stores a minimal amount of glucose yet relies almost completely on this substrate for energy generation[28,29]. The network architecture of brain microvasculature and astroglial perivascular end feet tightly couples glucose- and oxygen-flux rates with neuronal activity to minimize energy constraints[29]. Astrocytes contain small amounts of glycogen that could be converted to glucose under a nutrient shortage. In the

resting brain, glycolysis and oxidative phosphorylation rates match glucose and oxygen consumption. Brain stimulation causes transient uncoupling between them, which indicates the utilization of glucose through aerobic glycolysis. This disassociation is attributed to the compartmentalization of glycolysis and oxidative phosphorylation in different cell types in the brain. The astrocyte-to-neuron lactate shuttle (ANLS) hypothesis proposes that neuronal activity increases glycolysis specifically in astrocytes, which then leads to glucose to lactate conversion and the release of lactate that is taken up by neurons for mitochondrial ATP production (see reviews discussing the ANLS hypothesis[30,31]). Recently, the utilization of genetically encoded metabolic sensors allowed the ANLS hypothesis to be tested in acute brain slices and awake mice, which demonstrated direct glucose uptake by excitatory neurons upon stimulation[32]. However, the ANLS hypothesis and potential use of lactate as a fuel have not been studied systematically in other neuron subclasses, including inhibitory neurons, or at the neuronal processes.

The ability of neurons to modify or make new synaptic connections for memory formation requires a continuous supply of energy[12,33]. Under conditions of nutrient deprivation, neurons restrict energy use, which in turn results in weaker synaptic signalling between neurons and reduces precise information processing[34]. While glucose is the major fuel for neurons, ketone bodies and lactate could also be used for energy generation to adapt to glucose-starvation conditions and other anabolic pathways[20,35–37]. Notably, recent metabolite-tracing analysis in mammalian tissues argues that, even under starvation, the brain uses glucose as the preferred fuel for mitochondrial ATP production, synthesized from glycerol[38]. At the cellular level, neuronal mitochondria encompass a mechanism to sense glucose availability[39,40]. However, how neuronal mitochondria can tailor functional properties for alternative fuel use requires further investigation. Molecular mechanisms coupling nutrient flux, neuronal activity, and metabolism to sustain the immediate energy need, as well as the predicted future one, remain to be resolved.

Neuronal activity shapes synaptic energy metabolism

Neurons heavily rely on mitochondrial oxidative phosphorylation to meet their instant energy demands[10,11]. Therefore, in contrast to many cell types, neurons have evolved to master altering mitochondrial functions by rapidly promoting mitochondrial plasticity in response to neuronal activity. For maintaining energy homeostasis and neuronal functions, the precise axonal and dendritic distribution of mitochondria is essential[41–46].

Mitochondrial biogenesis peaks during axon growth and synaptogenesis in developing neurons[47] and regulates synaptogenesis[48]. As neurons mature, metabolism shifts from glycolysis to oxidative phosphorylation[47,49]. Selective immobilization of mitochondria is important for the extension and branching of neuronal axons and dendrites[50–53]. In fully developed neurons, approximately 50% of axonal mitochondria are located at the synapses[54] (Fig. 2). Although not all synapses contain mitochondria, the presence of mitochondria at the presynaptic terminals increases synaptic longevity[54,55]. At the resting state, maintenance of the neurotransmitter-filled synaptic-vesicle pool consumes a major part of basal presynaptic energy[56]. Perhaps this is why neurons still contain a large number of synaptic mitochondria when synaptic-vesicle release is inhibited[57].

At the postsynaptic site, dendritic spines rarely contain mitochondria in the resting state[58]. However, during synaptic transmission and plasticity, mitochondria may be transiently recruited into spines[59,60]. Mitochondrial network stability[14] and fission-and-fusion dynamics[61] are also essential for postsynaptic activity. At both the pre- and post-synapses, activity-driven mitochondrial positioning, form, and function are matched to the subcellular bioenergetic needs of neurons. The mechanisms that direct and retain mitochondria at the synapses will be discussed in the following sections.

Overall, it seems that mitochondrial energy metabolism is preferred under the basal state, while both glycolysis and oxidative phosphorylation are important to support 'on demand' ATP synthesis during synaptic transmission or plasticity[12,19,28,32]. Starting from glucose uptake to ATP production by mitochondria, multiple metabolic enzymes work together within the complex geometry of neurons. As a result of hundreds of interconnected reactions, nutrients are converted to energy and building blocks.

The inhomogeneous distribution of glucose transporters in vivo and in cultured neurons suggests that both the glucose supply and the enzymes of the pathway may be heterogeneously regulated[28]. Glycolytic enzymes and mitochondria can be shuffled to respond to nutrient fluxes and energy demands (Fig. 2b). Neuronal activity translocates glucose transporters to the presynaptic plasma membrane[28]. In addition, glycolytic enzymes colocalize to form metabolic pockets under stress at the presynaptic boutons[62,63]. This enhances local glucose influxes and promotes glycolysis at the energetically demanding pre-synapses. Increased glucose uptake and the compartmentalization of glycolysis, combined with the glucose-flux-dependent capture of mitochondria[39,40,64], might improve local metabolic efficiency, although these mechanisms were mostly investigated at the presynaptic regions.

The delivery and distribution of synaptic mitochondria Microtubule-based mitochondrial transport.

During neural development, a neuron grows extensive protrusions (neurites) from its cell body to form synaptic contacts with other neurons. Essential cargos for neurite and synaptic growth, including mitochondria, are delivered from the cell body through microtubule-based, long-range transport[65–67]. Mitochondria are first loaded onto microtubule motor–adapter complexes and are then transported out of the cell body, powered by the microtubule motors. In axons, microtubules are uniformly aligned, with all plus ends pointing to the axonal terminal and minus ends to the cell body; in dendrites, their polarities are mixed [68].

Kinesin motors mediate movement toward the plus ends of microtubules. Out of at least 14 kinesin families and 45 kinesin genes identified so far in mammals, the kinesin-1 family, also known as the conventional kinesin heavy chain (KHC) or KIF5, has been shown to be the primary motor for transporting mitochondria[69–72]. In addition, two members of the kinesin-3 family — KIF1Bα and kinesin-like protein 6 (KLP6) — are associated with mitochondria[73–75]. For moving mitochondria toward the minus ends of microtubules, cytoplasmic dynein is the universal motor [76].

Because these motor proteins are shared with other cellular cargos, molecular adapters are needed to allow the motors to recognize only mitochondria. To date, a diverse array of mitochondrial adapters has been discovered to anchor mitochondria to microtubule motors (Fig. 3a), indicating the versatile nature of the regulation under different circumstances. The best-characterized motor–adapter complex is the KHC–Milton–Miro complex (Fig. 3a). Milton (in mammals, TRAK1/Milton-1/OIP106 and TRAK2/Milton-2/GRIF1) is localized to mitochondria and interacts directly with KHC[77–79]. Importantly, kinesin light chain (KLC) seems to be dispensable for this complex[77]. Milton then binds to Miro, which has a carboxy-terminal transmembrane (TM) domain that is incorporated into the outer mitochondrial membrane (OMM)[80,81]. The kinesin and dynein complexes seem to coordinate with each other's activities and can reside on the same mitochondrion[76,82,83]. Although these mechanisms have been mostly studied in neurons, they may be shared with other cell types that use microtubule-based mitochondrial transport.

Synaptic-activity-mediated mitochondrial positioning.

Once mitochondria reach their final destinations in distal neurites, they are immobilized where needed most for supporting synaptic activity. Many mitochondria are unloaded from microtubules by increased concentrations of intracellular Ca^{2+} ions. Neuronal activity raises Ca^{2+} influxes at the synapses. Ca^{2+} binds to the EF hands of Miro, the mitochondrial adapter for both the kinesin and dynein motors (Fig. 3a), leading to conformational changes of the KHC–Milton–Miro complex and the dissociation of mitochondria from microtubules (Fig. 3b)[79,84–87]. Hijacking mitochondria in this manner close to synaptic membranes likely represents a temporary and local need for mitochondria, not only to rapidly meet the high energy demands required to maintain electric firing[19] and ion gradients across membranes, but also to buffer the burgeoning Ca^{2+} concentrations. This mechanism allows reversible and instantaneous regulation of mitochondrial motility. Once local Ca^{2+} ions are reduced, the KHC–Milton–Miro complex may resume its Ca^{2+}-free conformation and reattach to microtubules[79,84–87].

The far ends of synaptic terminals, such as dendritic spines and presynaptic boutons, are devoid of microtubules but enriched with actin filaments. During intense and repeated synaptic firing, mitochondria can be further guided into synapses by actin-mediated movement[88]. The actin motor, Myo19, anchors mitochondria to actin filaments through Miro (Fig. 3c)[89–91]. Neuronal membrane depolarization triggers actin-based acute translocation of mitochondria into dendritic spines[59]. The WASP family verprolin homologues protein 1 (WAVE1), which regulates actin polymerization, is critical for depolarization-induced mitochondrial movement into spines and filipodia and spine morphogenesis (Fig. 3c)[60]. In pre-synaptic boutons, electric activity can capture axonal mitochondria onto actin filaments through Myo6 and syntaphilin, triggered by the AMP-activated protein kinase (AMPK)–p21–activated kinase (PAK) energy signalling pathway[13] (Fig. 3c). These discoveries raise interesting questions that warrant further investigations. For example, does each synapse use a different set of myosin motor and adapter proteins to attract mitochondria? Or do these molecular players coordinate with each other?

Mitochondria located inside an active synapse may provide immediate service, yet those stationed within a short distance may function as energy reserves[13,14]. In postsynaptic dendrites, mitochondria are spatially confined (less than 30 μm) to local spines by both actin and microtubule cytoskeletons to support synaptic plasticity[14]. Similarly, in axons, mitochondria can be docked onto either microtubules through syntaphilin (Fig. 3b) or the actin network[13,92–94]. It is important to note that syntaphilin is an axon-specific protein[93]. Further dissection of neuronal-compartment-specific regulations of the motor–adapter complexes may illuminate how different populations of mitochondria are tethered and stabilized to cytoskeletal networks. How the transient mitochondrial hop-on-and-off mechanisms are coordinated at the synapses for different cytoskeletal tracks remains to be addressed.

Glucose-mediated mitochondrial localization.

Another key factor affecting activity-driven mitochondrial positioning at the synapses could be the fuel itself[95,96]. Glucose is metabolized to uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc), which is used for *O*-GlcNAc modification of Milton with the aid of O-linked *N*-acetylglucosaminyltransferase (OGT)[40,97]. Then, *O*-GlcNAcylated–Milton associates in the same complex with four and a half LIM domains protein 2 (FHL2), which docks mitochondria onto actin filaments[39] (Fig. 3d). In this way, mitochondria stay where glucose concentrations are higher to maximize their ability to use the fuel.

Notably, only 2–5% of total glucose is converted to UDP-GlcNAc through the hexamine biosynthetic pathway (HBP)[98]. How the catalytic activity of the rate-limiting enzymes for *O*-GlcNAcylation or the HBP flux is regulated by synaptic activity remains unanswered. Furthermore, how do mitochondria internally sense low levels of substrates for ATP production? When mitochondria need more fuel, there must be an inside-out signal coming from the internal mitochondria to either initiate movement to seek the fuel or have the fuel locally delivered. Once in the region enriched with glucose, mitochondria may be further immobilized by molecular mechanisms, such as FHL2-mediated docking (Fig. 3d). Although glucose is the main fuel for neurons, whether other fuel sources affect mitochondrial positioning is an important question to answer because it may provide mechanisms unique to glucose deprivation.

Additional regulators of mitochondrial motility.

The discoveries to date are probably only skimming the surface. A growing list of regulatory signals that could affect synaptic mitochondrial distribution has emerged, and their links to synaptic activity warrant further investigations. For example, hypoxia upregulated mitochondrial movement regulator (HUMMR) interacts with the KHC–Milton–Miro complex and regulates mitochondrial transport and distribution[99]. HUMMR is induced by hypoxia-inducible factor 1α and may enable mitochondrial entry into the distal part of the neurite or synapse during hypoxia. Interestingly, hypoxia also triggers glycolytic enzyme compartmentalization at the synapse[63]. Perhaps co-regulation of glycolytic and oxidative ATP synthesis pathways is critical for synaptic energy homeostasis in hypoxia.

Elevation of intracellular reactive oxygen species (ROS) immobilizes mitochondria in both fly and rat neurons through mechanisms potentially involving Miro and Milton[100–102]. Nitric oxide (NO) also arrests mitochondrial motility through unknown molecular mechanisms[103,104]. In addition, the ratio of ADP to ATP influences mitochondrial positioning in cultured neurons[5], which suggests another ‘sensing’ mechanism to attract mitochondria into the synapses in response to intense energy consumption. Besides neuronal activity and metabolites, neuromodulators can alter mitochondrial properties. Serotonin (5-HT) and dopamine (DA) have been shown to change mitochondrial movement in hippocampal neurons via the AKT–glycogen synthase kinase 3β pathway[65,105]. Focal nerve growth factor (NGF) stimulation can recruit mitochondria to the area of treatment[106,107]. Chronically, neuronal aging seems to slow mitochondrial motility by downregulating microtubule motor activities[108,109].

Future studies aimed at deciphering the interplay among different metabolic states, nutrient fluxes, neuromodulatory signals, and stressors that impact mitochondrial motility will shed more light on the synaptic energy blueprint. One major challenge ahead is how to precisely capture and accurately interpret these dynamic mitochondrial behaviours. A cultured neuronal system allows unambiguous discerning of neuronal polarities and application of various high-resolution live-imaging technologies, whereas an in vivo imaging system has the advantage of observing mitochondrial events during development and aging in an intact physiological environment.

It should be noted that the procedures to prepare live samples for both systems could cause damage to neurons or surrounding tissues, thus triggering signals to alter mitochondrial motility. In addition, the durations of imaging experiments, imaging medium compositions, neuron subtypes and locations chosen for imaging, and analytical methodologies could all make a difference in the final conclusions[6]. Combining complementary model systems, experimental conditions, and data-analysis strategies is key to making unbiased discoveries in the field.

Synaptic mitochondrial quality control

If getting mitochondria to the right place already seems to be a strenuous job, the ability of neurons to maintain a healthy pool of mitochondria at their far-reaching ends is unparalleled. Mitochondrial DNAs lack protection from methylation and are exposed to high levels of ROS[110]. Ca^{2+} and other ions, neurotransmitters, stressors, and toxins that accumulate inside the synapses as a result of neuronal activity, excitotoxicity, and aging make synaptic mitochondria prone to damage. Mitochondrial vulnerability is further exacerbated by the high energy requirements of neurons. Damaged mitochondria are not only detrimental locally at the synapse, but can also trigger systemic immune responses[111,112].

How the health of synaptic mitochondria is maintained both at steady state and under stress continues to be an important area for future research. A few key questions are of particular interest; for example, what type of mitochondrial quality control is implemented locally at the synapses, and is it regulated by synaptic activity and plasticity? In addition, how are

molecular players for quality control rapidly delivered to a damaged mitochondrion in a distal synapse, a long way from the cell body where new proteins are typically produced?

The remote locations of some synapses suggest that local protein translation is crucial for quality control[6,14]. Messenger RNAs may have already been delivered and stocked in the distal synapses, and once there is an urgent need for these proteins, translation can be initiated. It has been proposed that mRNAs of certain nuclear-encoded mitochondrial proteins are attached to the OMM[113–116]. Rapid local translation can supply newly minted mitochondrial proteins to rejuvenate old, damaged ones and maintain functional mitochondria[117]. Local protein supply may also adequately sustain the ubiquitin–proteasome system on the mitochondrial surface to remove defective OMM proteins or proteins stalled during import, or quickly provide mitochondrial proteases and chaperones to clear misfolded or denatured proteins inside the mitochondria (Fig. 4a)[118,119]. Local protein translation could further sustain key protein players that regulate the selective removal of faulty mitochondrial parts, including the generation of mitochondria nucleoid-enriched autophagosome (APs)[112], mitochondria-derived vesicles and compartments (MDVs and MDCs)[120–125], and structures positive for OMM (SPOTs)[126] (Fig. 4b), or could control mitophagy through which an entire mitochondrion is routed to lysosomes for degradation[6,116,127–129] (Fig. 4c).

Mitophagy is a type of mitochondria-selective autophagy and can occur in neurons both in vitro and in vivo[130–133]. The same set of autophagy machinery for initiation, expansion, and engulfment of damaged organelles[127] is employed during mitophagy, although additional molecular players are required (Fig. 4c). The best-studied mitophagy pathway is mediated by PINK1 and Parkin. Mitochondrial depolarization blocks the mitochondrial import of the Ser/Thr kinase PINK1, stabilizing it on the OMM. PINK1 subsequently phosphorylates multiple OMM proteins[134–137] and adjacent ubiquitin molecules[138–140], leading to the activation and recruitment of the cytosolic E3 ligase Parkin to the mitochondrial surface[141]. Parkin is further activated by PINK1's phosphorylation[141] and continues to ubiquitinate more OMM proteins, escalating the pathway. This feed-forward mechanism causes extensive phosphorylation and ubiquitination events on the mitochondrial surface, attracting the autophagy machinery[142] (Fig. 4c). Mitochondria can also be cleared by PINK1–Parkin-independent mitophagy pathways[6,129], as well as through non-selective macroautophagy[127].

Moreover, mitochondria may undergo dynamic fission-and- fusion at the synapses, like in most other types of cell, to discard, refresh, or exchange their contents[143] (Fig. 4d). Fission-and-fusion is mediated by mitochondrial membrane proteins: dynamin-related protein 1 (Drp1) and its receptors for fission, and mitofusin (MFN1 and MFN2) and optic atrophy 1 (OPA1) for fusion (see a recent review of fission-and-fusion mechanisms[144]).

In addition to local protein supply, anterograde microtubule-based transport may deliver more lysosomes, autophagosomes, or regulatory proteins packaged in vesicles from the cell body to support mitochondrial quality-control pathways. Damaged mitochondria could also be engulfed by autophagosomes locally at the synaptic terminal and then transported back to the soma[112,145], or simply spewed out of the synapses to adjacent non-neuronal scavenging cells for degradation[146,147].

The diversity of the surveillance mechanisms is well suited to the plasticity of synaptic mitochondria and opens a dialogue to address fundamental questions of how a distinct type of mitochondrial quality control arises at a unique synapse within an intact neuronal circuitry. For example, some MDVs appear under mild oxidative stress and preceding mitophagy, which is triggered by prolonged and excessive damage[120–122]. If both pathways were employed at distal neurites, there might be molecular sensors to switch one ‘on’ and the other ‘off’.

A recent study has shown that the biogenesis of certain types of MDVs depends on Miro for the initial microtubule-dependent protrusion of mitochondrial membranes[122] (Fig. 4b). By contrast, depolarization-triggered mitophagy requires proteasomal degradation of Miro to uncouple mitochondria from microtubules (Fig. 4c)[135,148–150]. Although Miro could serve as a molecular button to switch between these two quality-control pathways, the regulatory mechanisms remain to be resolved.

A neuron may need to make a prompt decision when a synaptic mitochondrion is damaged, considering all the factors of energetic expenses and metabolic needs, while trying to maintain its electric activity. Multi-disciplinary approaches, with scalable biosensors of mRNAs, newly synthesized proteins, ROS, metabolites, ATP, and sensitive reporters of the MDV, MDC, SPOT, and mitophagy pathways, in combination with super-resolution microscopy, individual-synapse stimulation with two-photon uncaging, and conventional electrophysiology techniques, will provide an excellent portfolio of tools to tackle these questions at a single-synapse resolution both in vivo and in cultured neurons.

Therapeutic potential of targeting synaptic mitochondria

Failure to maintain the synaptic energy blueprint is detrimental to neurons. Energy shortage and build-up of Ca^{2+} and ROS at individual synapses may lead to synaptic loss. The progressive loss of synaptic structure and function is an early sign prior to neurite retraction and cell death, and a shared signature among many neurodegenerative diseases, such as Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson’s disease (PD).

Human genetic studies have discovered variants in genes encoding mitochondrial membrane proteins that mediate mitochondrial trafficking, dynamics, and adaptation in various neurological disorders, such as encephalopathies (*DRP1* and *TRAK1*)[151,152], Charcot–Marie–Tooth disease type 2A (*MFN2*)[153], parkinsonism (*OPA1* and *MIRO*)[154–156], and autosomal-dominant optic atrophy (*OPA1*)[157]. Mutations in *PINK1* and *PARKIN*, whose products function in a linear axis to control the MDV[120,158] and mitophagy[159] pathways (Fig. 4b,c), cause early-onset, recessive forms of PD[160,161]. Moreover, variants in optineurin (*OPTN*) and *TBK1*, whose products mediate mitophagy (Fig. 4c), are associated with ALS[162]. The robust genetic evidence not only shows that failure to maintain mitochondria is a direct cause of neuropathology, rather than a consequence of other neuronal malfunctions, but also suggests that targeting these proteins and pathways may be effective for disease intervention.

Many of the neurodegenerative diseases involve age-dependent neuron loss. Mitochondrial function declines during brain aging with changes in proteome, lipidome, and metabolome[108,109,163]. Identification of early indicators or predictors of later-onset neurodegeneration, even before symptoms occur, will be especially valuable for early intervention to improve treatment efficacy. Changes in synaptic mitochondrial behaviours are very likely among the first signs of neuronal calamity and may be reflected at the molecular level. A molecular defect in neurons may be conserved in peripheral tissues, which could serve as an excellent candidate for biomarker development.

Recent studies have shown that Miro1 is resistant to mitochondrial depolarization-induced degradation in PD models, and this phenotype is retained across skin fibroblasts, induced pluripotent stem cells (iPSCs), and neurons derived from people with PD[148,149,164,165]. Importantly, although statistically the Miro1 defect is significantly associated with both people with PD and asymptomatic genetic carriers of the condition in large-cohort studies, it does not occur in every person with the disease or genetic carrier. Prolonged retention of Miro1 causes a delay in arresting and clearing damaged mitochondria, which then leads to oxidative stress and ultimately cell death of PD neurons[109,148–150]. Continued endeavours to search for molecular events that can mark the prodromal or early stage of a disease in a clinically accessible tissue (blood or skin) will enable more accurate patient stratification, improve the success of drug trials, and transform clinical care.

Emerging genetic and functional evidence has highlighted the therapeutic potential of targeting mitochondrial quality control to prevent or slow neurodegeneration. Substantial academic and industrial explorations of druggable targets to promote mitophagy, such as NAD+, Miro1, PINK1, and Parkin, are underway for diseases including PD, AD, and tauopathies[109,148,149,165–169]. Promising mitophagy-inducing compounds include NAD+ precursors[170], tomatidine[171], urolithin A[167], actinonin[167], kaempferol[168], rhapontigenin[168], Miro1 reducers[109,149], and many others[169], through diverse mechanisms of action.

It is important to note that the best therapeutic outcomes can be guided only by a deeper understanding of the basic molecular principles governing synaptic mitochondrial homeostasis, especially in an in vivo setting. Ensuing efforts to strengthen basic scientific knowledge and enhance technological innovation will empower more rigorous translational research to provide treatment strategies for people with disease.

Closing remarks

The study of mitochondrial heterogeneity and homeostasis mechanisms in neurons is significant at many levels. Protein players regulating mitochondrial motility and distribution are probably conserved among multiple cell types. Lessons learnt from neurons may shed light on similar mechanisms that are crucial for other cell types and on how these mechanisms are used for specialized purposes in heterogeneous tissues. For example, mitochondria redistribute to the posterior part of lymphocytes during their migration to possibly fuel cellular mobility[16]. Similarly, during the migration and invasion of breast cancer cells, mitochondria move to the leading edge of the cell, and blocking this movement can compromise the metastatic ability of cancer cells[172]. Mitochondria can even travel

from cell to cell, through nanotubes or vesicles, for a wide range of purposes, from supporting mitochondrial functions of recipient cells to relieving stress responses of donor cells[125,146,147,173–176]. Diversity in other molecular components (such as players that regulate lipidome, proteome, and stress pathways) could contribute to additional differences in mitochondrial functions and physiology required to meet specific cellular demands. These molecular mechanisms that confer mitochondrial heterogeneity warrant further investigation.

Many questions are ripe to be answered. Particularly, how are mitochondria immobilized in distinct subcellular compartments? What signals dictate mitochondria to permanently stay, pause, or move? Does an active synapse prefer to recruit a mitochondrion that is on or off microtubules? How do mitochondrial ATP-production pathways work together with glycolytic enzymes at the synapses? How is mitochondrial damage cleared or mended at the distal synapses?

Further investigations of subcellular domain-specific mechanisms, such as the concentrations and dynamics of Ca^{2+} ions and metabolites, the interactions of the resident motor–adapter complexes with actin and microtubule networks, compartmentalized metabolic enzymes, and local machinery for protein translation and membrane structure formation, might be key to solving these questions. In addition, system-level research on the coordination of synaptic mitochondria with neuronal signalling pathways, neuron–glia interactions, and local brain vasculature dynamics will reveal the impact of mitochondrial adaptations at the organismal level. We are now presented with an unprecedented opportunity to divulge how intrinsic and extrinsic cellular instructions integrate to distribute and sustain distinct mitochondrial populations. Intervening in these processes provides opportunities to promote the health of the cell and the cellular network, such as the nervous system, and to fend off cellular pathologies to ameliorate human illnesses.

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Box 1 |

Glossary

Action potential: The rapid rise and subsequent decline in neuronal membrane voltage resulting from the opening of ion channels. It propagates along the axon of a neuron leading to the spread of electric activity within milliseconds.

Astroglial perivascular end feet: The specialized structure of an astrocyte (a star-shaped glia cell found in the nervous system) that ensheaths blood vessels, providing structural support and allowing direct metabolite exchange between blood vessels and astrocytes.

Dendritic spine: A small membrane protrusion from the postsynaptic dendrite of a neuron that receives presynaptic input from neighbouring axons.

Presynaptic boutons: Specialized swellings at the end (terminaux) or along (en passant) the axonal branches, which contain synaptic vesicles filled with neurotransmitters and other supporting organelles, where a synapse is formed with another neuron.

Synapse: A specialized structure that allows communication between two neurons, where the presynaptic bouton of one neuron comes into close apposition to a postsynaptic neuron to pass electrical or chemical signals.

Synaptic plasticity: The activity-dependent alterations of pre-existing synapses to modify the strength or efficacy of synaptic transmission.

Synaptic transmission: The process through which a presynaptic neuron communicates with a postsynaptic neuron across a synapse.

Synaptic-vesicle recycling: At the presynaptic boutons, synaptic vesicles undergo a cycle of exocytosis, release of neurotransmitters, endocytosis, refilling of synaptic vesicles with neurotransmitters to sustain the synaptic vesicle pool, and moving to the site of exocytosis. This cycle is essential to maintain synaptic transmission.

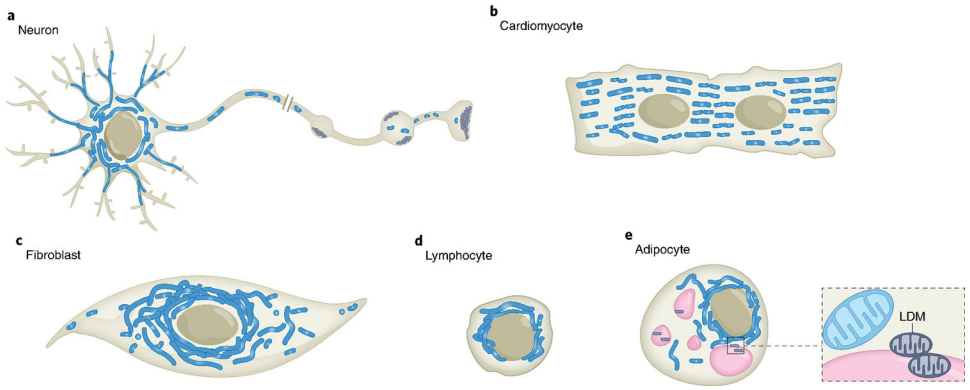

Fig. 1 |. Mitochondrial network in different cell types.

The shape and composition of the mitochondrial network are tailored to match cell-type-specific energy demands. **a**, In neurons, mitochondria form a long and connected network at the somatodendritic region. In contrast, axonal mitochondria occupy a smaller volume as discrete units. **b**, In cardiomyocytes, mitochondria form a dense and perfectly aligned network and occupy >30% of the cytoplasmic volume[177]. **c**, Mitochondria are largely distributed evenly in fibroblasts, forming an interconnected network near the nucleus and a smaller motile pool at the cell periphery[4]. **d**, In lymphocytes, mitochondria are relatively homogeneously distributed in a small cytoplasmic volume. Mitochondrial network and size change in response to polarization and activation for metabolic adaptation[15,16]. **e**, In adipocytes, mitochondria occupy most of the cytoplasmic volume. Subpopulations of metabolically specialized mitochondria (grey; LDM) are associated with lipid droplets (pink)[9].

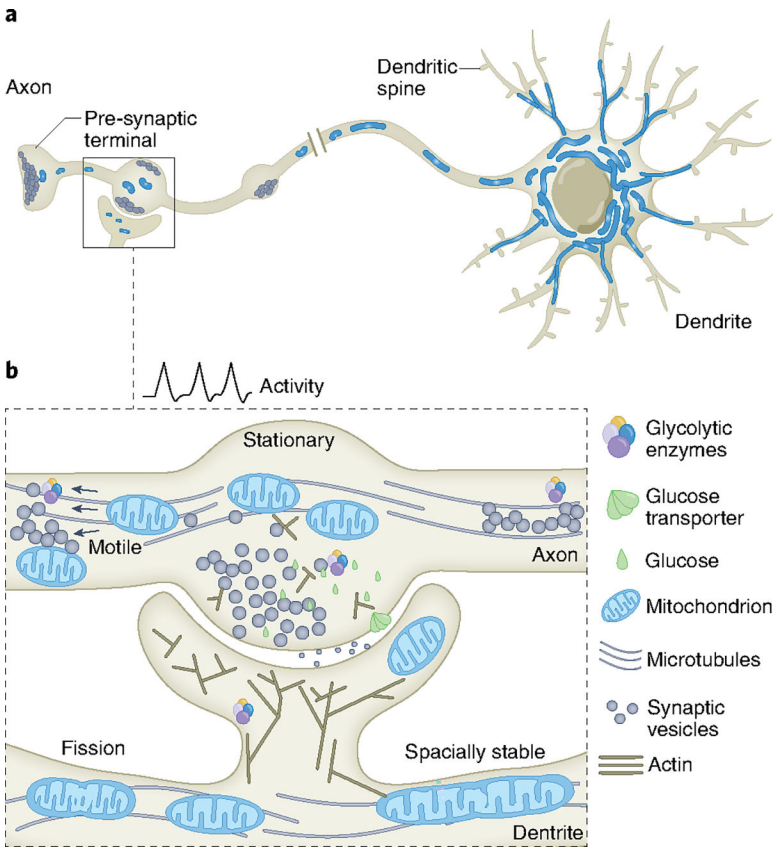

Fig. 2 |. Mitochondrial morphology and localization in neurons.

a, A typical neuron, composed of a cell body (soma), dendrites with multiple dendritic spines, and an axon with presynaptic boutons. **b**, Scheme depicting a synapse. Synaptic mitochondria locally generate ATP to sustain synaptic activity. The localization of mitochondria at the synapses is regulated by microtubule-based long-distance axonal transport and actin-based capture mechanisms. In addition to mitochondria, activity-dependent glucose uptake and local glycolysis enzymes support synaptic ATP synthesis.

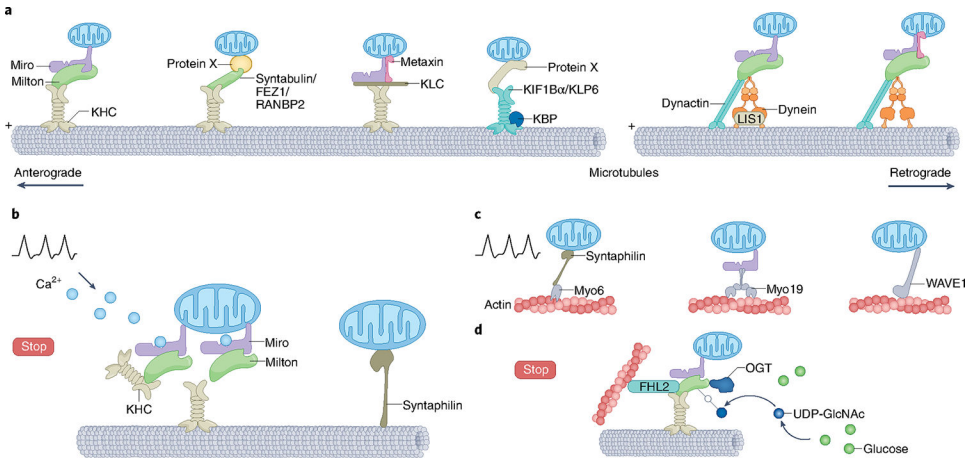

Fig. 3 |. Molecular mechanisms underlying mitochondrial trafficking and positioning.

a, Schematic representation of currently known molecular machineries for microtubule-based mitochondrial movement. Besides Miro and Milton, several other proteins have been found to recruit KHC to mitochondria, which include syntabulin[178], fasciculation and elongation protein-zeta 1 (FEZ1)[179,180], and RAN-binding protein 2 (RANBP2)[181]. Miro, metaxin (a group of OMM proteins), and KLC can form a complex to aid in KHC-dependent mitochondrial movement[182]. Both KIF1Bα and KLP6 can interact with KIF1-binding protein (KBP)[74], which is essential for mitochondrial localization[75,183]. Miro–Milton–dynein acts as the core motor–adapter complex for retrograde movement[82,182]. **b**, Mechanisms underlying mitochondrial arrest. High Ca^{2}+ influxes as a result of synaptic activity dissociate mitochondria from microtubules by changing the conformation of the KHC–Milton–Miro complex[79,84]. In axons, syntaphilin can anchor axonal mitochondria onto microtubules close to presynaptic boutons[13,92]. **c**, Synaptic activity drives mitochondria into presynaptic boutons or postsynaptic spines via actin-mediated movement. **d**, Mitochondria stay where glucose concentrations are higher via Milton–OGT–FHL2-mediated docking.

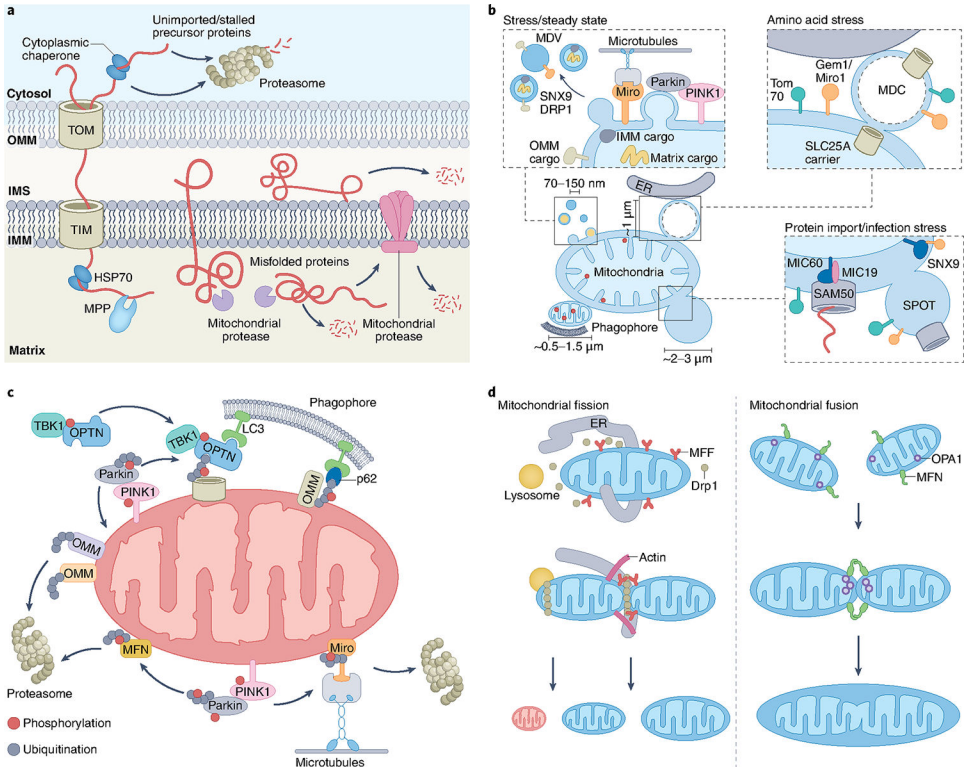

Fig. 4 |. Mitochondrial quality-control pathways.

Future research is needed to unravel which quality-control pathways are implemented at individual synapses. **a**, Misfolded or defective mitochondrial proteins can be repaired or cleared by mitochondrial proteases, chaperones, or the ubiquitin–proteasome system. OMM, outer mitochondrial membrane. IMM, inner mitochondrial membrane. IMS, intermembrane space. **b**, Piecemeal removal. Mitochondrial stress can be alleviated and damaged mitochondrial portions can be removed by the biogenesis of mitochondrial-derived vesicles (MDVs) during various stress responses or at steady state[120–122,124,125], mitochondrial-derived compartments (MDCs) under amino acid stress[123], structures positive for OMM (SPOTs) under protein import or infection stress[126], or mitochondrial nucleoid-enriched autophagosomes (APs) under the basal condition[112]. ER, endoplasmic reticulum. **c**, The entire damaged mitochondria can be digested through mitophagy[129]. The scheme shows one mitophagy pathway that is dependent on PINK1 and parkin. **d**, Mitochondria also undergo fission-and-fusion to discard or exchange materials[143,144,184]. MFF, mitochondrial fission factor. Figures adapted with permission from: **a**, ref. [185], Springer Nature Limited; **b**, ref. [186], Cell Press; **c**, ref. [129], Springer Nature Limited; **d**, ref. [187], Elsevier.