REVIEW

Transporting mitochondria in neurons [version 1; referees: 2 approved]

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Abstract

Neurons demand vast and vacillating supplies of energy. As the key contributors of this energy, as well as primary pools of calcium and signaling molecules, mitochondria must be where the neuron needs them, when the neuron needs them. The unique architecture and length of neurons, however, make them a complex system for mitochondria to navigate. To add to this difficulty, mitochondria are synthesized mainly in the soma, but must be transported as far as the distant terminals of the neuron. Similarly, damaged mitochondria—which can cause oxidative stress to the neuron—must fuse with healthy mitochondria to repair the damage, return all the way back to the soma for disposal, or be eliminated at the terminals. Increasing evidence suggests that the improper distribution of mitochondria in neurons can lead to neurodegenerative and neuropsychiatric disorders. Here, we will discuss the machinery and regulatory systems used to properly distribute mitochondria in neurons, and how this knowledge has been leveraged to better understand neurological dysfunction.

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Introduction

The transport of mitochondria is critical to a neuron's health. Although frequently referred to as "the powerhouse of the cell", mitochondria do much more than produce ATP. In addition to being the cell's major energy provider, mitochondria are responsible for storing and buffering Ca^{2+}, detoxifying ammonia, and producing some steroids[1], heme compounds[2], heat, and reactive oxygen species. They are vital to the metabolism of neurotransmitters glutamate and gamma-aminobutyric acid (GABA)[3], and send signals for apoptosis, proliferation, and cell survival[4]. They even boast their own DNA and protein synthesis machinery as a vestige of their previous life as bacteria. It is thus unsurprising to learn that precise control of mitochondrial number, health, and distribution is especially critical to the neuron, which is a complex cell with high energy and regulatory demands.

Several features distinguish neurons from other cells. First, they have a long, thin axon—the longest axon in the human body can extend over one meter—and contain many areas of subspecialization, like the pre-synapse, post-synapse, growth cones, and nodes of Ranvier[5], each with different metabolic needs. Second, as the carriers of synaptic information, neurons have ever-changing energy and Ca^{2+} buffering demands, especially at their terminals. Finally, because neurons are post-mitotic and will stay with the organism for the duration of its life, they must be protected from excitotoxicity and kept in a state of homeostasis as long as possible. The appropriate allocation and sustenance of mitochondria are essential to fulfilling the many demands of the neuron, and keeping it in good health.

To meet the vacillating needs of neurons, about 30% to 40% of these spry organelles are in motion at any given time[6–9]. Properly distributing mitochondria throughout a neuron, however, is complicated by the fact that mitochondria are primarily produced in the soma, with most of their proteins encoded by nuclear DNA, but are needed as far away as the synaptic terminal. Static mitochondria pool at or near synapses, which may be important for rapid neuronal firing, while passing mitochondria may be recruited to support prolonged energy needs and repetitive neuronal firing[10–12]. Additionally, damaged mitochondria produce reactive oxygen species, which can be toxic to the cell, and these dysfunctional mitochondria must be repaired by fusing with new mitochondria transported from the soma, be returned to the soma for degradation in a process termed mitophagy, or be cleared through mitophagy in neurites *in situ*[13]. Whether providing a service to the neuron, or needing clearance to prevent damage to the neuron, mitochondria must travel long distances and know precisely where and when to stop. When their transport machinery breaks down or signals regulating this machinery cannot be relayed, the consequence can be injury to or even death of the neuron[9,14–17]. Here we will review the molecular mechanisms underlying mitochondrial transport in neurons, and what happens when they are disrupted.

Transport machinery

Much like a train, organelle transport requires a track, a motor, and a cargo. For mitochondria—the cargo—the overwhelming majority of their tracks are microtubules, which in mammalian neurons have their plus ends oriented toward the axon terminal, and their minus ends toward the soma (although this homogeny is not the case in dendrites)[18–20]. This uniform polarity makes neuronal axons an especially useful model for studying organelle transport. The motors used to transport mitochondria depend on the direction in which they need to travel. In general, mitochondria move in the anterograde direction (away from the soma) using a family of kinesin motors, and move in the retrograde direction (toward the cell body) using the dynein motor[21]. While kinesins and dynein are also used to carry other cargos, the motor adaptors that anchor the motor and cargo together are cargo-specific, allowing for the regulation of movement by particular cellular signals. In addition to microtubules, mitochondrial movement can be powered along actin filaments by myosin motors, a process that is required for short-range movement, and for opposing movement along the microtubules[22–24].

Anterograde movement with the kinesin heavy chain complex

The best-characterized mitochondrial transport complex to date uses kinesin heavy chain (KHC, a member of the kinesin-1 family) as its motor, and Miro and milton as its motor adaptors. Miro stands for "mitochondrial Rho" and belongs to the atypical Rho (Ras homolog) family of GTPases (RhoT1/2 in mammals). Miro is anchored to the outer mitochondrial membrane (OMM) via its carboxy-terminus transmembrane domain. Miro binds to milton (trafficking protein, kinase-binding, or TRAK1/2 in mammals), which in turn binds to the carboxy-terminus of KHC[25–27]. Milton was identified in a *Drosophila* screen for blind flies and was named after the great poet and polemicist John Milton, who was also blind[28]. Together, Miro and milton facilitate anterograde mitochondrial movement along microtubules by connecting mitochondria to KHC (Figure 1a). When either Miro or milton is mutated in animal models, mitochondria are trapped in the soma and lose the ability to move out into the axons[9,14–16,26,28].

Miro and milton are not the only adaptors that can link mitochondria and KHC. Syntabulin can bind directly to the OMM and KHC, and disruption of syntabulin function has been shown to inhibit the anterograde transport of mitochondria in neurons[29]. Similarly, disrupting fasciculation and elongation protein zeta-1 (FEZ1), and RAN-binding protein 2 (RANBP2) also affects mitochondrial distribution because of their association with kinesins, possibly KIF3A and KIF5B/C, respectively[30–34].

Mutations in KHC have been shown to reduce anterograde mitochondrial movement but do not eliminate it entirely, which suggests that other kinesin motors may also play a role in anterograde mitochondrial motility[21]. For example, kinesins from the Kinesin-3 family KIF1Bα and KLP6 may interact with KIF1 binding protein (KBP) to transport mitochondria[35–38]. KIF1B can transport mitochondria along microtubules *in vitro*, and mutations in *Klp6* inhibits anterograde mitochondrial motility into neurites; however, the roles of these other kinesins await further clarification.

Retrograde movement with the dynein complex

Dynein is thought to act as the retrograde motor for microtubule-based mitochondrial movement, although far less is known about the mechanisms underlying its action. In contrast to the host of

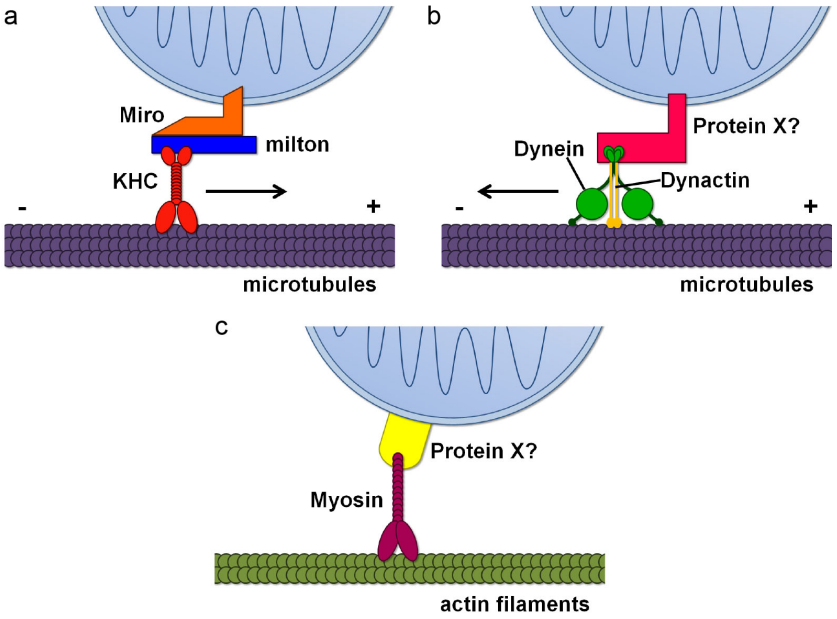

Figure 1. Schematic representation of mitochondrial transport machinery. (**a**) The primary motor/adaptor complex mediating anterograde mitochondrial transport along microtubules (purple), including kinesin heavy chain (KHC) (red), Miro (orange), and milton (blue). (**b**) The machinery mediating retrograde mitochondrial transport along microtubules (purple), including dynein (green), dynactin (gold), and a potential motor adaptor, Protein X (pink). Protein X could be the milton/Miro complex[39]. (**c**) Mitochondrial movement along actin filaments (olive), using a myosin motor (fuschia) and a potential motor adaptor, Protein X (yellow).

kinesins available for anterograde transport, there is only one identified dynein motor; however, dynein's larger and more complex structure has made it difficult to study. Dynein has been shown to form a complex with dynactin, and this complex has been shown to also interact with milton/TRAK2 and with Miro[39], which lends support to dynein's role in mitochondrial transport (Figure 1b). Interestingly, dynein movement is also thought to depend on kinesin-1, as mutation in kinesin-1 reduces retrograde movement of mitochondria[21].

Actin-based movement with myosin complexes

A small though not insignificant number of mitochondria are also transported along actin filaments[22]. This is more common in actin-enriched neuronal compartments, like growth cones, dendritic spines, and synaptic boutons. Myosins are actin-based motors, and the myosin Myo19 has been shown to anchor directly to the OMM, and regulate mitochondrial motility[24, 40]. Myosins V and VI have also been shown to play a role in mitochondrial motility by opposing microtubule-based mitochondrial transport[23], although whether these myosin motors attach directly to mitochondria or require a motor adaptor remains unknown (Figure 1c). WAVE1 (WASP family verprolin homologous protein 1), which regulates actin polymerization, has been shown to be critical for mitochondrial transport in dendritic spines and filopodia—areas that are actin-rich—and therefore may be involved in the actin-based transport of mitochondria[41].

Anchoring mitochondria

If 30% to 40% of mitochondria are in motion at any given time, then more than half of mitochondria are static. While understanding of how stationary pools of mitochondria are generated is still nascent, one protein, syntaphilin, stands out. Syntaphilin serves as a molecular brake, docking mitochondria by binding to both the mitochondrial surface and to the microtubule[42]. Both kinesin-1 and the dynein light chain component LC8 have been shown to regulate this mechanism[43,44]. Intriguingly, a recent study using optogenetics has shown that the mitochondrial dance between mobility and stabilization depends on the balance of forces between motors and anchors, rather than all-or-none switching[45].

Regulation of the kinesin heavy chain/milton/Miro complex

Ca^{2+}

The ability of mitochondria to temporarily stop where they are needed is just as important as their ability to move. When cytosolic Ca^{2+} concentration is elevated, Ca^{2+} binds to the EF hands of Miro and triggers a transient and instantaneous conformational change in the KHC/milton/Miro complex. This conformational change causes dissociation of either the whole complex from microtubules[9], or KHC from mitochondria[17], which arrests movement of mitochondria. When Ca^{2+} concentration is lowered, Ca^{2+} is removed from Miro, and mitochondria are reattached to microtubules by the complex and can start moving again. The sensitivity of mitochondrial movement to Ca^{2+} is likely a means by which mitochondria can be recruited to areas of high metabolic demand or low local ATP, like post-synaptic specializations and growth cones. During glutamate receptor activation, mitochondria are recruited where Ca^{2+} influx is increased, which confers neurons with resistance to excitotoxicity[9,17]. Interestingly, brain-derived

neurotrophic factor (BDNF) has recently been shown to arrest mitochondrial motility via Ca^{2+} binding to Miro1 in cultured hippocampal neurons[46].

Glucose

Glucose has recently been shown to influence mitochondrial motility via the KHC/milton/Miro complex. The small sugar UDP-GlcNAc is derived from glucose through the hexamine biosynthetic pathway. UDP-GlcNAc is affixed to milton by *O*-GlcNAc transferase (OGT), in a process called *O*-GlcNAcylation[47]. Extracellular glucose concentration or OGT activity can modulate mitochondrial motility through *O*-GlcNAcylation of milton. This mechanism links nutrient availability to mitochondrial distribution, which could be a mechanism by which neurons maintain a balanced metabolic state.

PINK1/Parkin

When mitochondria are severely damaged, they undergo mitophagy, a crucial cellular mechanism that eliminates depolarized mitochondria through autophagosomes and lysosomes. Damaged mitochondria must be stopped prior to the initiation of mitophagy. To accomplish this, mitochondrial depolarization activates PINK1 (PTEN-induced putative kinase 1)-mediated phosphorylation of Miro[16,48], which subsequently triggers Parkin-dependent proteasomal degradation of Miro, thus releasing the mitochondria from its microtubule motors[16,49]. It is likely that stopping mitochondria in this manner is an early step in the quarantine of damaged mitochondria before degradation. In fact, this PINK1-mediated phosphorylation of Miro has been shown to protect dopaminergic neurons *in vivo* in *Drosophila*[50]. PINK1 and Parkin can also work in concert to remove damaged mitochondria through local mitophagy in distal axons, which would obviate the need for the mitochondria to be transported all the way back to the soma, and instead require the recruitment of autophagosomes to the damaged mitochondria[13]. How a cell chooses between transporting a mitochondrion back to the soma or using local mitophagy when it is damaged in the axon remains an outstanding question.

The dynamics of mitochondrial fission and fusion also plays a central role in PINK1/Parkin-mediated mitophagy. For example, mitofusin, a large GTPase that regulates mitochondrial fusion, is a target of the PINK1/Parkin pathway. Degradation of mitofusin prevents mitochondria from being able to fuse, and they instead fragment, a critical step prior to mitophagy[51–55]. An in-depth discussion of the role of mitochondrial dynamics in quality control merits its own review, and an excellent F1000 Faculty Review and two others are recommended in the References section[56–58].

Other milton/Miro regulators

In humans, milton is encoded by two different genes: *TRAK1* and *TRAK2*. It has been reported that TRAK1 binds to both kinesin-1 and dynein, while TRAK2 predominantly favors dynein[39]. In *Drosophila*, milton has several splicing variants, one of which (milton-C) does not bind to KHC[26]. These varying forms of milton may play an important role in regulating the KHC/milton/Miro complex.

Another regulator that merits mentioning is HUMMR (hypoxia up-regulated mitochondrial movement regulator), whose expression is induced by hypoxic conditions. HUMMR has been shown to interact with the KHC/milton/Miro complex, and increases the ratio of anterograde to retrograde movement of mitochondria[59]. Similarly, a family of proteins encoded by an array of armadillo (Arm) repeat-containing genes has been shown to bind to milton/Miro and regulate mitochondrial motility[60].

It is worthwhile to note that mitochondrial fission and fusion also affect mitochondrial motility. The same mitofusin mentioned previously also binds to milton/Miro, and knockdown of mitofusin 2 has been shown to inhibit mitochondrial motility[61]. Additionally, transient fusion has been shown to promote mitochondrial movement[62].

Other regulators

The list of possible mitochondrial transport regulators burgeons daily, although thorough mechanisms remain scarce. For example, nerve growth factor can cause accumulation of mitochondria to its site of application[63,64]. Another growth factor, lysophosphatidic acid, can inhibit mitochondrial movement[65]. Intracellular ATP levels regulate mitochondrial motility, which decreases when close to synapses, and local production of ADP can recruit more mitochondria to areas requiring more ATP[66,67]. Increased cAMP can increase mitochondrial motility[68]. Pharmacological activation of AMP-activated protein kinase (AMPK) can promote anterograde movement of mitochondria for the formation of axon branches[69]. Activation of the serotonin receptor increases mitochondrial movement via the AKT-GSK3β (Akt-glycogen synthase kinase 3β) pathway[6], and conversely, dopamine and activation of the dopamine receptor D2 can inhibit mitochondrial movement via the same AKT-GSK3β pathway[70,71]. One recent study shows that GSK-3β directly regulates dynein[72], while another study shows that it promotes anterograde movement[68]. This list of molecules likely skims the surface of all the signals and sensors involved in mitochondrial motility, which are yet to be uncovered.

Implications for neurological disorders

Because mitochondria are critical for energy production, calcium buffering, and cell survival pathways, it is not surprising to learn that impaired mitochondrial movement has been linked to neuronal dysfunction and neurological disorders[73–75]. The long distance travelled by mitochondria in neurons, as compared to in other cells, may account for the fact that neurons are more vulnerable to impairments in mitochondrial transport. Altered mitochondrial motility may provide an early indication of neuronal pathology prior to cell death, either because motility is directly affected or because it is altered as a consequence of other mitochondrial malfunctions.

Neurodegenerative diseases

Aging itself has been shown to decrease neuronal mitochondrial motility in mice, and several age-dependent neurodegenerative diseases have been linked to mitochondrial motility defects[76]. Mutations in the previously mentioned *PINK1* and *Parkin* are

both causes of familial Parkinson's disease (PD)[77,78]. In individuals lacking either functional PINK1 or Parkin, a failure to isolate, stop, and remove the damaged mitochondria may contribute to neuronal cell death. Unpublished work using patients' samples from our laboratory also suggests that neurodegeneration in non-*PINK1/Parkin*-related PD cases may arise in a similar manner, and that stopping damaged mitochondrial motility is neuroprotective. This finding highlights the broader implications of mitochondrial motility in neuronal health and pathology.

The pathological forms of amyloid beta and tau, the chief markers of Alzheimer's disease (AD), have both been shown to inhibit mitochondrial motility in several AD models[79–83]. Superoxide dismutase 1, soluble (SOD1), fused in sarcoma (FUS), C9orf72, and TAR DNA-binding protein 43 (TDP-43) mutations, which cause familial amyotrophic lateral sclerosis (also called Lou Gehrig's disease), have also been shown to impair mitochondrial transport in mice, flies, and cultured neuronal models[84–91]. Mutant huntingtin protein, with the polyglutamine expansions characteristic of Huntington's disease etiology, can act to "jam traffic" by mechanical obstruction, and may also bind to milton or even to the mitochondria itself to disrupt mitochondrial motility[92–94]. Mutations in *mitofusin 2* causing Charcot-Marie-Tooth disease alter mitochondria movement[95], and finally, mitochondrial motility defects have also been observed in models of hereditary spastic paraplegia, a disease characterized by axonal degeneration[96,97].

Neuropsychiatric disorders

A few psychiatric disorders have also been linked to mitochondrial motility defects. Mutations in disrupted in schizophrenia 1 (*DISC1*) may contribute to both schizophrenia and some forms of depression[98]. DISC1 complexes with TRAK1/milton and Miro1 to modulate anterograde transport of mitochondria[99,100], and its interactors NDE1 and GSK3β have recently been recently shown to associate with TRAK1/milton and similarly play a role in mitochondrial motility[68]. DISC1 also interacts with the previously mentioned FEZ1[101], which binds to kinesins[25,28]. Among several causes, depression can be attributed to a loss of serotonin[102]. Interestingly, the application of serotonin to cultured hippocampal neurons has been shown to increase mitochondrial motility[6].

Closing remarks

The proper transport of mitochondria in neurons is critical to the homeostasis of the cell. Many questions in this field, however, remain to be answered. On a basic level of investigation, a more thorough understanding of the machinery—like the dynein motor, myosin motors, and the signals and adaptors that regulate this complex system—is still desperately needed.

A significant higher-level question is: how does the cell decide what to do with a damaged mitochondrion in the distal segment of an axon? The cell has several options: return the mitochondria to the soma for lysosomal degradation, which requires long-distance retrograde transport; degrade the mitochondrion via local mitophagy, which requires recruitment of autophagosomes to mitochondria and fusion of autophagosomes with lysosomes in the axon; or send a healthy mitochondrion from the soma via anterograde transport to repair the damage by fusing with the unhealthy mitochondrion. Could this decision be made on the basis of the nature or severity of the damage to the mitochondrion? Does this decision take into account the relative energy expended? What are the signals and molecules that execute this decision? These actions must also be influenced by the local metabolic state, *de novo* protein synthesis, and neuronal activity in extremities far from the cell body.

It is also crucial to explore the translational implications of these findings. What of this knowledge can be leveraged for therapeutic benefit? Perhaps mitochondrial motility could be used as a novel phenotypic readout to screen for more effective treatments for neurological disorders, as well as a way to diagnose the disease and monitor its progression. A more comprehensive understanding of the molecular mechanisms underlying mitochondrial transport will prove invaluable as it provides novel targets, like the KHC/milton/Miro complex, for diagnostic innovation and therapeutic intervention.

Most knowledge of mitochondrial movement in neurons has been uncovered using cultured rodent neurons. The application of emerging *in vivo* models will shed light on the physiological significance of the regulation of mitochondrial motility[76,103–107]. Therefore, imaging mitochondria in living animals, especially during development and aging, as well as under disease conditions, will be an important step for the field.

Finally, given the inseparable relationship between neuronal function and metabolism, and mitochondrial motility and distribution, their underlying regulatory mechanisms must be interwoven. How do action potentials, neuronal signaling molecules like dopamine and serotonin, or metabolites like glucose, fatty acids, nd amino acids influence mitochondrial motility and distribution? And how do mitochondrial motility and function reciprocally control neuronal homeostasis? Answers to these questions will reveal how neurons respond to changes in their activities and environments by regulating this cellular linchpin.

Competing interests

The authors declare that they have no competing interests.

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