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REVIEW

Mitochondrial dynamics, positioning and function mediated by cytoskeletal interactions

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Abstract

The ability of a mitochondrion to undergo fission and fusion, and to be transported and localized within a cell are central not just to proper functioning of mitochondria, but also to that of the cell. The cytoskeletal filaments, namely microtubules, F-actin and intermediate filaments, have emerged as prime movers in these dynamic mitochondrial shape and position transitions. In this review, we explore the complex relationship between the cytoskeleton and the mitochondrion, by delving into: (i) how the cytoskeleton helps shape mitochondria via fission and fusion events, (ii) how the cytoskeleton facilitates the translocation and anchoring of mitochondria with the activity of motor proteins, and (iii) how these changes in form and position of mitochondria translate into functioning of the cell.

Keywords Mitochondrial dynamics · Cytoskeleton · Microtubules · Molecular motors · Mitochondria

Introduction

Mitochondria are double-membraned organelles that are involved in a multitude of processes including generation of adenosine triphosphate (ATP), thermogenesis, intra-cellular Ca^{2+} homeostasis, reactive oxygen species (ROS) production, apoptosis and stem cell differentiation [1–6]. The outer mitochondrial membrane (OMM) is a relatively smooth lipid bilayer, whereas the inner mitochondrial membrane (IMM) folds inward to form structures known as cristae [7, 8]. The region between the two mitochondrial membranes is the intermembrane space [7]. The OMM allows the exchange of metabolites between the intermembrane space and the cytosol while the IMM contains the electron transport chain (ETC) proteins, and encloses the mitochondrial matrix, where signalling processes including the Kreb's cycle, β-oxidation and ROS production take place [9, 10].

In living cells, mitochondria appear as tubular, interconnected networks, which change shape by undergoing fission and fusion (Fig. 1). These fission–fusion dynamics are crucial to the maintenance of mitochondrial quality and energy production in the cell. OMM fusion is regulated by mitofusin 1 and mitofusin 2 (MFN1 and MFN2) while fission is mediated by the dynamin-related protein 1 (DRP1) [11, 12]. MID49, MID51 and mitochondrial fission factor (MFF) recruit DRP1 to the OMM [13]. In budding yeast, the OMM protein, Fis1p promotes mitochondrial fission by recruiting the DRP1 homolog Dnm1p to mitochondria [14]. Human Fis1 (hFis1/Fis1) also binds DRP1 with ER proteins at the mitochondria-ER interface during mitochondrial fission [15]. hFis1 binds to and inhibits the GTPase activity of MFN1, MFN2, and the IMM fusion regulator optic atrophy 1 (OPA1) thereby giving rise to a more fragmented mitochondrial network [16]. hFis1 induces DRP1-dependent mitochondrial fission by forming mitochondria-ER contacts that trigger mitochondrial calcium influx [17]. Intriguingly, in absence of the hFis1 domain responsible for mitochondria-ER tethering, mitochondria cluster near the nucleus, indicating that hFis1 potentially maintains mitochondrial organisation by also modulating mitochondrial transport [16].

IMM fusion and fission are carried out by two different forms of OPA1. Two IMM peptidases namely OMA1 and YME1L1 proteolytically cleave OPA1 to form the long, transmembrane form and short, soluble forms of OPA1 (L-OPA1 and S-OPA1, respectively) and this aids

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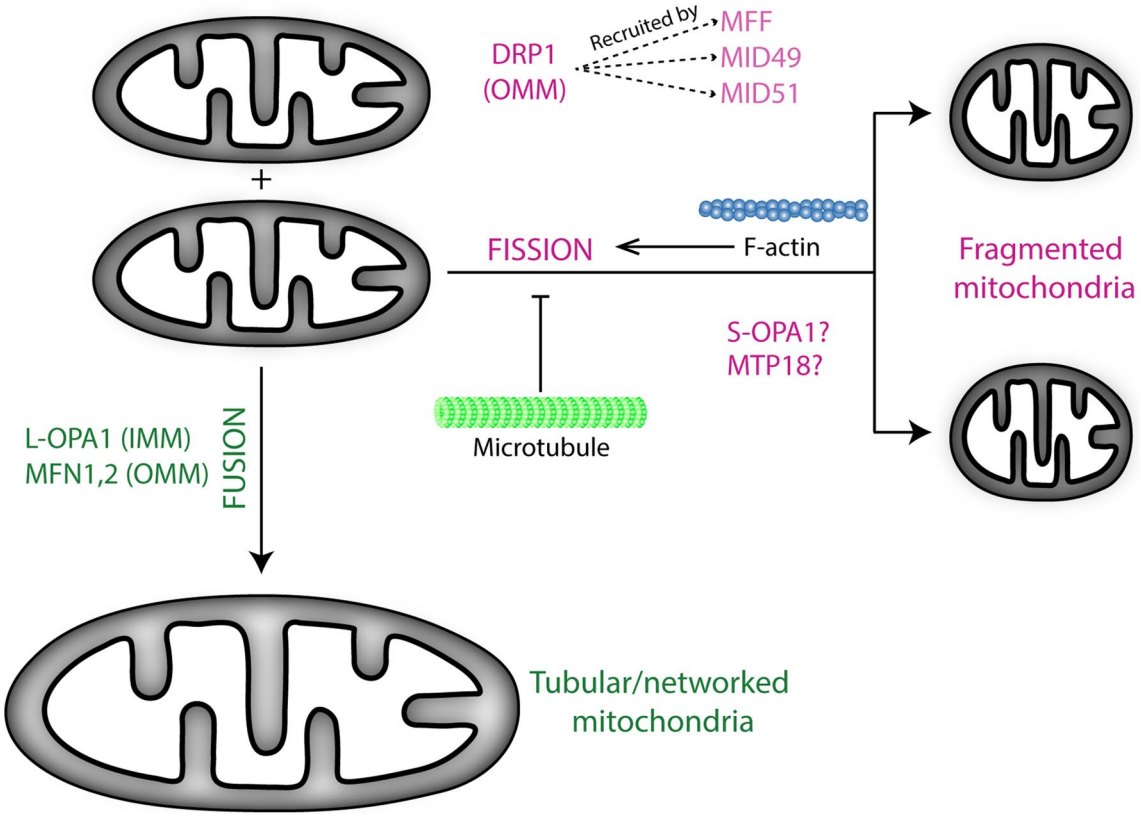

Fig. 1 Overview of the players involved in effecting mitochondrial dynamics. Mitochondrial fission is mediated by DRP1, which is recruited by MFF, MID49 and MID51. Fission is inhibited when mitochondria are associated with microtubules. Mitochondrial fusion is brought about by L-OPA1, MFN1 and MFN2. F-actin and its associated proteins enable mitochondrial fission. S-OPA1 and MTP18 induce mitochondrial fission

the membrane fusion activity of Opa1 [18–20]. The membrane anchoring of L-OPA1 to the mitochondria-specific lipid cardiolipin is sufficient for IMM fusion [21]. Stoichiometric levels of S-OPA1 mediate fast membrane fusion [20] thus, loss of OPA1 function results in fragmentation of the mitochondrial network [22]. Interestingly, increased levels of S-OPA1 downregulates fusion, however, the precise mechanism through which this occurs remains unknown [20, 23]. Another IMM protein, MTP18 fragments mitochondria when over-expressed, and results in hyperfusion of mitochondria when depleted [24]. The expression of MTP18 correlates with DRP1-mediated fission. While MTP18 is present at the IMM, it lacks conserved IMM motifs or domains. Thus, the role of MTP18 as a ubiquitous IMM fission protein has not been fully established.

The functional requirements of a cell correlate with changes in mitochondrial dynamics, form and positioning. For instance, brown adipocytes display fragmented mitochondrial networks through the activity of DRP1 and cleavage of OPA1 in response to adrenergic stimulation to enable the transition from nutrient oxidation to thermogenesis [25]. On the contrary, maintenance of tubular networks of mitochondria by astrocytes during neuroinflammation is necessary for astrocyte survival [26]. Dividing cells exhibit fragmented mitochondria, with the increase in mitochondrial number reducing partitioning error during independent segregation of mitochondria into daughter cells [27, 28]. Additionally, during meiotic cell division, mitochondria are anchored to the poles of *Schizosaccharomyces pombe* zygotes to enable uniparental inheritance of mitochondria [29]. The transport and accumulation of mitochondria to specific compartments in neurons is crucial for their functioning [30–34]. Thus, variability in mitochondrial form and localisation in response to the function or metabolic state of the cell maintains mitochondrial and cellular health [35, 36].

Recent research has demonstrated that the cytoskeleton regulates mitochondrial dynamics, positioning and function within the cell. The cytoskeleton in eukaryotic cells consists of actin filaments (F-actin), microtubules, intermediate filaments and septins. F-actin is assembled from G-actin and is mediated by actin nucleators and crosslinkers such as formins, fascin and Arp2/3 [37]. F-actin can form higher order flexible structures that organise into linear bundles, two-dimensional networks and three-dimensional gels [34].

F-actin is widely distributed throughout cells, forming a range of cytoskeletal structures of varying functions. Specifically, actin filaments nucleated from inverted formin-2 (INF2) facilitate mitochondrial fission, while fascin-bound actin filaments form filopodia which a cell uses to probe its environment [38, 39]. Actin networks shape the surface of the cell, provide mechanical stability to the cell and participate in cytokinesis and help in cell locomotion [40–42].

Myosins are F-actin-based motor proteins important for their role in muscle contraction and responsible for actin-based motility through ATP hydrolysis [43]. F-actin is involved in regulating mitochondrial fission, positioning and ROS production, and non-muscle myosin II has been implicated in mitochondrial fission [44–52].

Microtubules are dynamic, hollow filaments which help direct intracellular transport, form the mitotic spindle during cell division, and direct the position of organelles within the cell [53–55]. Microtubules typically emerge from the microtubule-organising centre (MTOC), where their minus-ends are capped. Microtubules require the minus and plus-end directed motor proteins, cytoplasmic dynein (henceforth dynein) and kinesin, respectively, to generate forces and move cargo along cytoskeletal tracks [43]. Microtubules inhibit fission of associated mitochondria and act as tracks for mitochondrial transport and anchorage [27, 56–61].

Intermediate filaments (IFs) are non-polar structures that provide mechanical strength to a cell and anchor organelles [62, 63]. IFs also affect mitochondrial morphology, organisation, membrane potential and lipid composition [64–69]. The three cytoskeletal filaments—F-actin, microtubules and the IFs are crosslinked by plectin [70, 71]. Plectin alters mitochondrial size and ROS production [72, 73]. Septins are a unique component of the cytoskeleton that assemble into non-polar filaments forming bundles, rings and cage-like structures that aid in the organisation of compartments inside cells [74]. Septins have also been observed to alter mitochondrial form [75].

The cytoskeleton is a key determinant of mitochondrial dynamics

Mitochondrial fission and fusion dynamics play an essential role in maintaining mitochondrial health and survival. Mitochondrial fission is proposed to help remove damaged mitochondria through mitophagy, stimulate mitochondrial DNA replication and biogenesis, while mitochondrial fusion aids the spread of metabolites, enzymes and mitochondrial gene products within the mitochondrial network as well as dilutes the effects of damaged mitochondria during ageing [76–78]. During the early stages of *Drosophila* oogenesis, a reduction of MFN induces mitochondrial fragmentation which aids the removal of damaged mitochondrial DNA (mtDNA) by mitophagy proteins [77, 78]. On the other hand, mitochondrial fusion safeguards differentiated skeletal muscles from accumulation of mtDNA point mutations and deletions [78]. Deletion of MFN1 and MFN2 leads to severe depletion of mtDNA in skeletal muscles and causes muscle atrophy in mice [78]. Taken together, the maintenance of fission–fusion balance is important for mitochondrial function and thereby cell survival. Here, we describe how the cytoskeleton facilitates, and in some instances, dictates mitochondrial fission–fusion dynamics.

F-actin facilitates mitochondrial fission

F-actin plays a key role in mitochondrial fission by aiding the activity of DRP1 (Fig. 2) [39]. Mitochondrial fission occurs when DRP1 oligomers form ring-like structures around the OMM, leading to constriction and eventual fission of the mitochondrion [79]. However, mitochondrial circumferences are often wider than the diameter of DRP1 rings [80]. Thus, F-actin enables the pre-constriction of mitochondria at mitochondria-ER contacts, thereby decreasing the mitochondrial cross-sectional diameter and enabling DRP1-mediated scission [44, 45]. The presence of F-actin is sufficient to increase DRP1 activity in vitro, possibly, because F-actin aids the maturation of DRP1 oligomers to form functional rings around the mitochondria [46]. Thus, deletion of the actin-depolymerising protein, cofilin1 leads to accumulation of DRP1, which then induces mitochondrial fragmentation [81]. However, another study showed that while the down-regulation of cofilin through RNAi resulted in increased accumulation and association of DRP1 with mitochondria, it led to elongated mitochondria, likely due to the abrogation of DRP1-independent steps in mitochondrial fission [82].

Mitochondrial morphology and dynamics are also regulated by actin-associated proteins. The depletion of the actin-nucleating protein INF2 leads to the loss of F-actin, and results in increased mitochondrial lengths [83]. Subsequent work showed that another actin nucleator, Spire1C and INF2 together form short actin filaments that localise at mitochondria-ER contacts [84]. These short filaments generate forces required to tighten ER tubules around the mitochondrial circumference [85]. The actin-based motor proteins non-muscle myosin II (myosin IIA and myosin IIB) are likely responsible for this tightening since they localise to mitochondria-ER sites, and upon depletion lead to longer mitochondria [52]. Recently, the non-muscle myosin isoform IIC (NMIIC) was also implicated in aiding mitochondrial fission [86]. A mutation in the gene that encodes for NMIIC hinders mitochondrial fission and alters the organisation of the mitochondrial genome [86]. This mutation is also linked to peripheral neuropathy and hearing loss, suggesting a possible role for aberrant mitochondrial dynamics in these disease states [86]. INF2-mediated actin polymerisation enhances

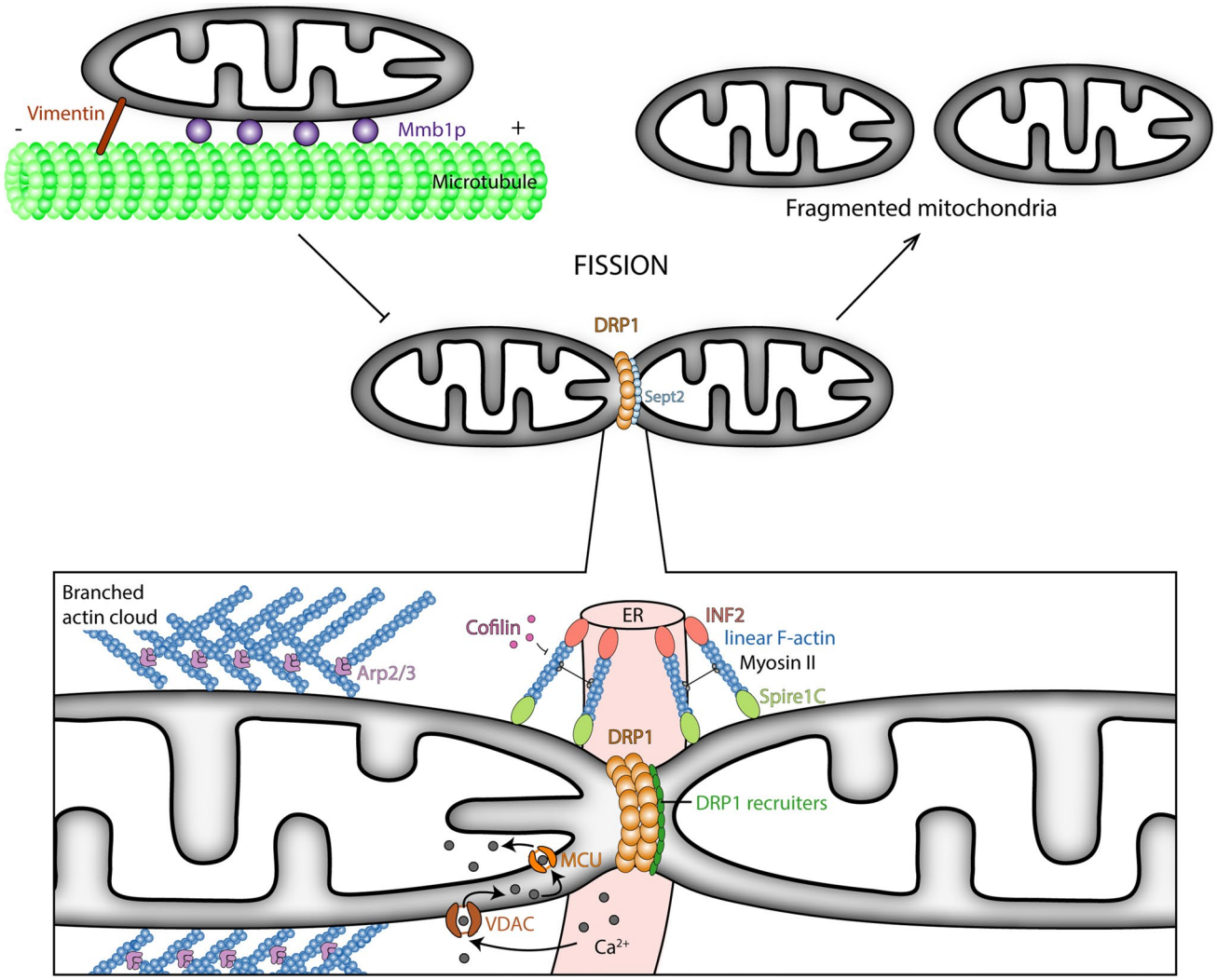

Fig. 2 The cytoskeleton and its associated proteins regulate mitochondrial dynamics. DRP1-mediated mitochondrial fission is inhibited when mitochondria are bound to microtubules via Mmb1p and vimentin. DRP1 binds directly to Sept2 and other recruitment factors at mitochondrial fission sites. F-actin aids mitochondrial fission at mitochondria-ER contact sites along with INF2, Spire1C and myosin II. Cofilin inhibits F-actin-mediated mitochondrial fission. DRP1-independent IMM constriction is enhanced through increased supply of calcium from the ER to the mitochondrial matrix via the VDAC and MCU. Arp2/3-mediated branched actin clouds also induce mitochondrial fission independent of the ER

the percentage of mitochondria-ER contacts about two-fold upon ionomycin stimulation, which increases the supply of calcium from ER stores to the mitochondrial matrix through the voltage-dependent anion channel (VDAC) and mitochondrial calcium uniporter (MCU) [87]. This in turn activates IMM constriction through ETC activity in a DRP1-independent manner [87].

Actin has also been implicated in mediating stress-induced mitochondrial fission through the transient assembly of F-actin on hyperfused regions of the OMM aided by the actin branching protein, Arp2/3 [82]. The actin assembly promotes DRP1 recruitment followed by rapid fission over 3–5 min [88]. The ability of Arp2/3 to form these transient actin structures possibly aids the rapid increase in mitochondrial fission observed during mitotic prophase [82].

Attachment of mitochondria to microtubules inhibits mitochondrial fission

In eukaryotic cells, microtubules and mitochondria physically associate with each other [27, 57, 89, 90]. Transmission electron microscopy revealed that α- and β-tubulin localise to mitochondrial membranes and immunoprecipitation experiments confirmed that they specifically associate with the VDACs on the OMM [91]. Since then, the importance of microtubules and associated proteins in maintaining

mitochondrial morphology, dynamics, and health has been explored in more detail.

Disruption of microtubule assembly decreases mitochondrial motility, thereby affecting mitochondrial fission and fusion [92]. In *Dictyostelium discoideum* cells, depolymerisation of microtubules using the drug nocodazole reduces both mitochondrial fission and fusion [56]. In *S. pombe*, depolymerisation or destabilisation of microtubules amplifies mitochondrial fragmentation due to an increase in the rate of mitochondrial fission [27, 57–59]. Conversely, reduction in the frequency of microtubule catastrophe results in longer microtubules and thereby, longer mitochondria due to decreased mitochondrial fission rates [27].

Recent studies have identified how microtubule-associated proteins (MAPs) modulate mitochondrial form and dynamics. One such example is the microtubule-associated tumour suppressor 1 (MTUS1), which normally localises to the OMM via MFN1 and MFN2 [93]. The depletion of MTUS1 results in shorter and more rounded mitochondria, indicating a role for this MAP in maintaining the fission–fusion equilibrium [93]. In *S. pombe*, deletion of the microtubule–mitochondria linker protein, Mmb1p results in unopposed mitochondrial fission indicating that the attachment of mitochondria to microtubules is important in inhibiting Dnm1-(yeast DRP1) mediated fission [27].

Intermediate filaments and other cytoskeletal proteins participate in mitochondrial dynamics

Fluorescence microscopy, subcellular fractionation and immunoprecipitation assays revealed that the IF vimentin directly binds to mitochondria [64]. Depletion of vimentin results in mitochondrial swelling and fragmentation [64]. Interestingly, this depletion also significantly reduces levels of α-tubulin in the mitochondrial fraction, indicating that vimentin possibly mediates the interaction of mitochondria with microtubules [64].

Septins and other cytoskeleton-associated proteins such as plectins also cause alterations to the mitochondrial morphology [72, 75]. In skeletal myoblasts, one of the four plectin isoforms namely, P1b, links IFs to mitochondria [72]. Loss of P1b upregulates MFN2, thereby causing a substantial increase in the width of mitochondrial z-disk wrapping [72]. However, whether P1b directly associates with MFN2 and the mechanism through which P1b alters mitochondrial morphology remain unknown.

A member of the septin family, Septin 2 (Sept2) binds directly to DRP1 and localises to a subset of mitochondrial constriction sites. Depletion of Sept2 decreases DRP1 localisation to the OMM resulting in hyperfused mitochondria [75]. Silencing another member of the septin family, Septin 7 (Sept7) also resulted in the formation of hyperfused mitochondria possibly because depletion of Sept7 co-depletes Sept2 [75]. The precise mechanism through which these septins promote the recruitment of DRP1 to fission sites remains elusive.

The cytoskeleton is required for mitochondrial transport and anchorage

Mitochondrial positioning typically involves immobilisation of mitochondria at specific sites by attachment to either the cytoskeleton or membranes via anchor proteins. Prior to immobilisation, mitochondria are often actively transported to the sites of anchorage by motor proteins on polar cytoskeletal tracks. In addition to fission–fusion dynamics, regulated positioning plays a central role in maintaining the organisation and functioning of the mitochondrial network.

Dynamic mitochondrial organisation is crucial in highly active cells such as neurons, muscle cells, and secretory cells, and during events with high energy demands such as cell division, migration, injury, and differentiation [27, 29, 94–99]. Triggered by intracellular cues, mitochondrial transport and anchorage in concert likely help achieve the required organisation of the mitochondrial network to provide energy that drives these cellular functions and events. Denser populations of mitochondria within a cell maintain elevated ATP to ADP ratios [96]. Thus, mitochondrial positioning shapes energy gradients within the cell to meet localised energy demands. Concurrently, high energy consumption results in increased local ADP levels and facilitates mitochondrial transport to these sites [100]. Similarly, Ca^{2+}-sensing proteins regulate mitochondrial positioning and motility in regions of high Ca^{2+-}signalling activity to buffer calcium levels in the cell.

Actin-based transport of mitochondria is predominantly observed in several plant cells, and some fungi and insects [62, 101, 102]. Microtubule-based movement, on the other hand, is the main mode of mitochondrial transport in cells of protists and animals such as *D. discoideum, D. melanogaster*, and mammals [56, 60, 103, 104]. In addition to microtubule-based, long-range transport of mitochondria, neurons of several organisms employ actin-based transport for short-range movement and docking of mitochondria at pre-synaptic terminals [47, 48, 105–107]. Anchorage of mitochondria is also brought about by association with microtubules and IFs in various organisms. Here, we detail how the cytoskeleton and its associated proteins maintain mitochondrial organisation in the cell by mediating mitochondrial transport and anchorage.

Mitochondria rely on F-actin and associated proteins for their organisation

While most mammalian cells rely on actin filaments for mitochondrial anchorage, actin dynamics has been implicated in the movement of mitochondria during interphase

and mating in *Saccharomyces cerevisiae* [108, 109]. The myosin type V motor Myo2 associates with mitochondria through adaptor proteins to effect mitochondrial movement on actin cables [110–113] (Fig. 3a). Independent of motors, Arp2/3-mediated actin dynamics also aids the transport of mitochondria to the bud [108]. Mitochondrial recruitment of Arp2/3 proteins initiates F-actin assembly to provide forces for transport of mitochondria towards the bud [108, 114–116] (Fig. 3a). The plant myosin XI family is closely related to the fungal and metazoan myosin V family, and its members transport mitochondria on F-actin tracks [117, 118]. The unconventional myosin Myo19 has been proposed to play a role in transporting mitochondria on F-actin, as Myo19 overexpression increases mitochondrial velocities [119] (Fig. 3b). Myo19 localises to mitochondria by association with atypical mitochondrial Rho GTPases (Miro proteins), or independently by virtue of the motor's tail domain [120–122].

In addition to mitochondrial transport, Myo19 is likely involved in actin-based mitochondrial docking [119, 123, 124] (Fig. 3b). Myo19 is required to form starvation-induced filopodia in cultured cells, with the motor subsequently localising to mitochondria enriched at these filopodia [123]. Depletion or overexpression of Myo19 causes perinuclear aggregation of mitochondria, indicating a role for Myo19 in organising the mitochondrial network [121]. Metaphase and anaphase organisation of mitochondria is also dependent on Myo19, with loss of Myo19 resulting in failure of cytokinesis [125].

Myosin V and VI possess calmodulin-binding domains and have been proposed to promote mitochondrial docking in mammalian cells as they oppose microtubule-based transport of mitochondria in cultured neurons [106] (Fig. 3c). Additionally, myosin VI motors are recruited to ubiquitin on damaged mitochondria directed for mitophagy by Parkin, via myosin's ubiquitin-binding domain [126]. These motors in turn trigger the regulated assembly of actin filaments to form cages around the damaged mitochondria, likely to prevent their movement and fusion with other mitochondria [126] (Fig. 3b).

The role of F-actin in maintaining mitochondrial organisation is apparent in neurons and muscle cells. F-actin-mediated anchorage prevents the movement of a third of the stationary axonal mitochondria in neurons [48]. Stimulation of axons with nerve growth factor (NGF) is correlated with mitochondrial transport to NGF foci, and subsequent F-actin-dependent docking of mitochondria [47]. F-actin associated proteins have been implicated in maintaining

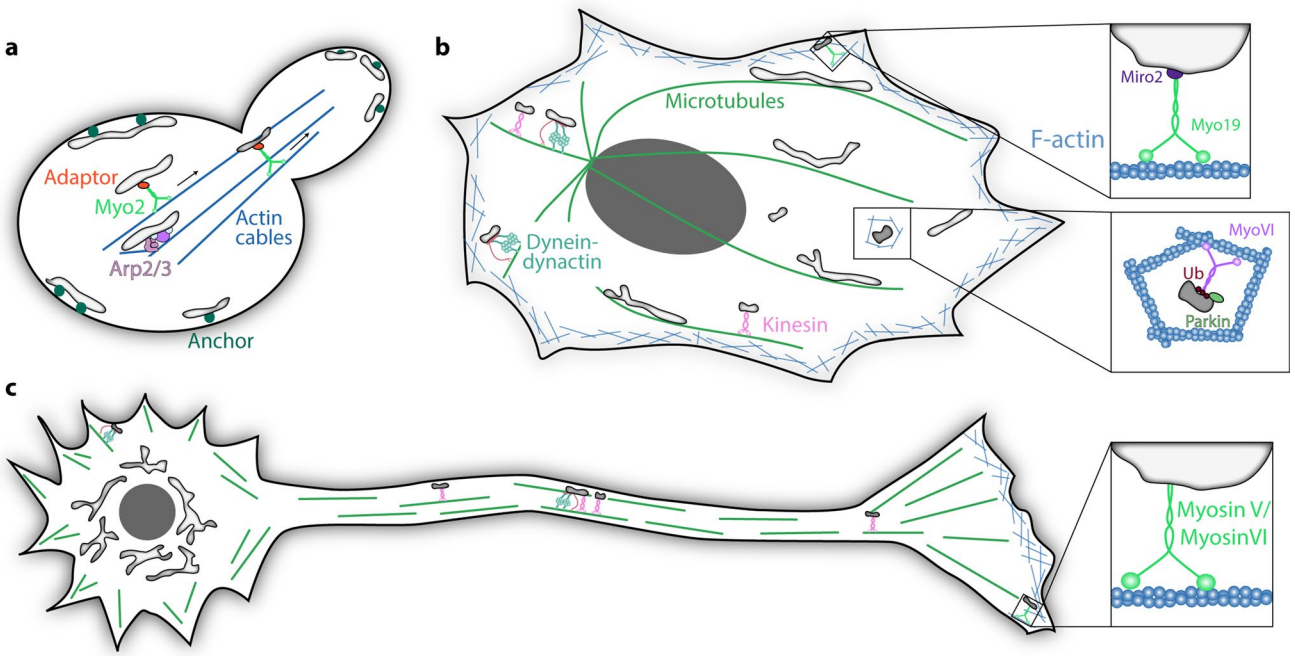

Fig. 3 F-actin and myosin motors participate in mitochondrial transport and anchoring. **a** The motor protein Myo2 and Arp2/3-mediated actin dynamics help transport mitochondria into the bud in *S. cerevisiae*. Mitochondria are additionally tethered along the cortex via anchor proteins. **b** In addition to the microtubule-based machinery, actin-based motors also participate in mitochondrial distribution. Myo19 associates with mitochondria either directly or via Miro proteins to organise mitochondria at the cell periphery and transport mitochondria on F-actin. Myosin VI is recruited onto mitophagy-destined mitochondria by ubiquitin, in order to isolate damaged mitochondria by triggering the formation of actin-cages around them. **c** Myosin V and VI have been implicated in activity-dependent anchorage of axonal mitochondria

mitochondrial organisation in fly and worm muscle cells [127–129]. Cofilin and regulated Arp2/3 activity are also involved in maintaining mitochondrial arrangement in these cells [129–131].

Mitochondria are transported by kinesins and dyneins, and anchored by tether proteins on microtubules

Microtubule plus-end directed transport of mitochondria is enabled by the kinesin-1 (KIF5) family of motor proteins [60]. On the other hand, dyneins drive minus-end directed mitochondrial transport [60]. Adaptor proteins Milton and Miro, first discovered in *Drosophila*, link these motors to mitochondria to regulate their bidirectional transport on microtubules [132, 133]. Milton interacts with Miro, which localises to the OMM through its single-pass, C-terminal transmembrane domain [104, 134, 135]. The N-terminal coiled-coil domain of Milton interacts with kinesin-1 heavy chain, thereby recruiting the motor to mitochondria by the Miro-Milton association [104].

Vertebrates have two Milton and Miro orthologues each—trafficking kinesin protein (TRAK) 1, TRAK2, and Miro1, Miro2, respectively [60, 136]. In neurons, TRAK1 binds to both kinesin-1 and the motor-adaptor complex dynein–dynactin, and mainly localises to axons [137]. On the other hand, TRAK2 predominantly localises to dendrites and binds to the dynein–dynactin complex as it adopts a conformation which precludes kinesin-1 binding [137]. TRAK2 requires Miro1 to enable minus-end directed transport of mitochondria in fibroblasts, but can also regulate plus-end directed transport in the absence of Miro1 when KIF5C is overexpressed [120]. Interestingly, TRAK1 and TRAK2 localise to mitochondria even in the absence of Miro1 and Miro2 [120].

Miro1 associates with dynein to facilitate redistribution of mitochondria towards the repositioned MTOC in response to immune-cell activation [138]. Miro1 also associates with kinesin-1 to transport mitochondria on astral microtubules to the cytokinetic furrow during late anaphase [103] (Fig. 4a). However, in late cytokinesis, mitochondria are passively transported along growing microtubule tips in a motor-independent process due to the association of Miro with the + TIP protein CENP-F (Fig. 4b) [139, 140]. Mitochondrial localisation of CENP-F is enhanced by the overexpression of Miro1 [140]. Expression of truncated CENP-F defective for mitochondrial localisation increases perinuclear aggregation of mitochondria, indicating a role for the Miro-CENP-F association in distributing mitochondria within the cell [141].

Mitochondrial motility in both axons and dendrites is unaltered in the absence of Miro2, but is reduced with the loss of Miro1 [142] (Fig. 4c, d). However, about a third of microtubule-dependent mitochondrial transport is preserved in the absence of both Miro1 and Miro2 [120, 142]. Together, these studies underscore the importance of Miro in regulating bidirectional mitochondrial transport, but also hint at the existence of Miro-independent mechanisms of mitochondrial motility and TRAK recruitment (Fig. 4e, f). So far, these mechanisms have been found to involve kinesin-1 adaptor syntabulin and mitochondrial fusion proteins. Syntabulin associates with mitochondria via its C-terminal domain to regulate mitochondrial organisation in a Miro/TRAK-independent manner [143, 144] (Fig. 4e). Acute loss of syntabulin lowers mitochondrial densities in distal processes, reduces anterograde mitochondrial motility, and impairs synaptic transmissions and presynaptic short-term plasticity in neurons [144, 145].

Co-immunoprecipitation experiments evinced that MFN2 interacts with Miro and TRAK proteins to maintain mitochondrial motility [146]. MFN1 recruits TRAK proteins to mitochondria in fibroblasts lacking Miro proteins [147] (Fig. 4f). Conversely, microtubule-based transport is likely necessary for fission–fusion dynamics of mitochondria [94]. Could the 'tug-of-war' interaction between kinesin and dynein motors attached to the same mitochondrion lead to opposing forces that constrict the mitochondrion? This constriction could then enable the recruitment of DRP1 to the OMM in a mechanism similar to that of actin-mediated constriction and fission.

Microtubules are not only necessary for long-range transport, but also for activity-dependent anchorage of mitochondria. About two-thirds of axonal mitochondria are immotile and stably associated with microtubules [48, 148, 149]. The microtubule-mitochondria linker protein Mmb1p suppresses microtubule dynamicity and stably tethers mitochondria to microtubules in *S. pombe* [57]. Microtubules are essential for the maintenance of mitochondrial organisation in human cardiomyocytes [150]. The Ca^{2+}-sensing EF-hand domains of Miro proteins make them particularly important for activity-dependent reorganisation of the mitochondrial network. Mutations in the EF-hand domain of Miro1 result in a loss of activity-dependent anchorage of mitochondria in neuronal and astrocytic processes [151, 152].

Syntaphilin, a microtubule-binding protein, associates with mitochondria through two C-terminal, OMM-targeting domains [149]. Axonal mitochondria are anchored to microtubules by syntaphilin when Ca^{2+} binding by Miro triggers syntaphilin to bind to KIF5 and displaces the motor from the Miro-TRAK complex [149, 153] (Fig. 4g). Mitochondrial enrichment at growth cones is also dependent on syntaphilin-mediated docking [154]. Demyelinated neurons have more stationary mitochondria docked with syntaphilin, to cope with the increased energy demand associated with the loss of saltatory conduction [155]. Loss of mitochondrial immobilisation in the absence of

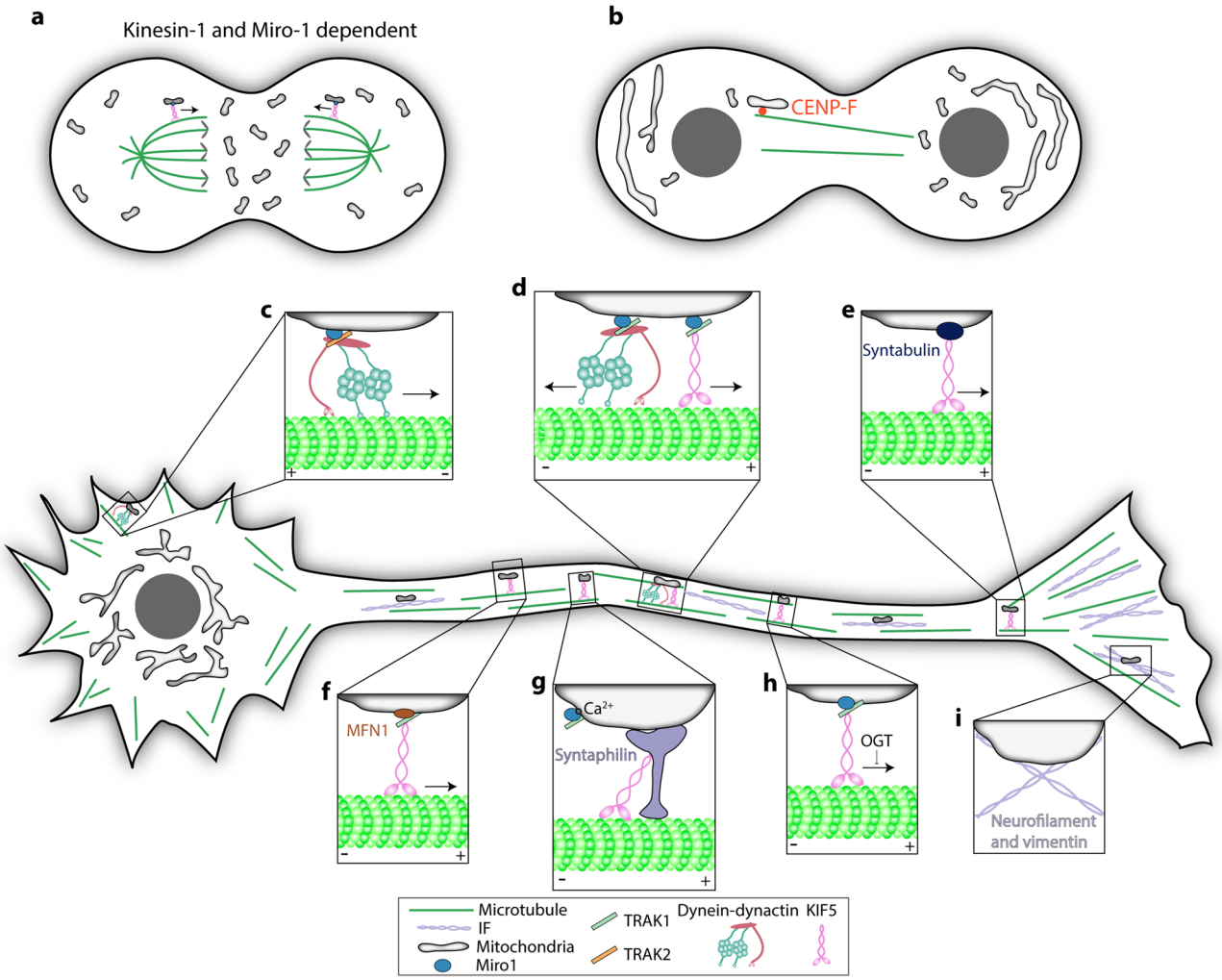

Fig. 4 Role of microtubules and intermediate filaments in the transport and anchorage of mitochondria. **a** Kinesin-1 transports mitochondria by the Miro-TRAK association on astral microtubules to the cytokinetic furrow during late anaphase. **b** Miro associates with CENP-F to transport mitochondria along growing microtubule plus-ends during late cytokinesis. **c** Dendritic mitochondria are predominantly transported on microtubules by the dynein–dynactin motor-adaptor complex which is recruited to mitochondria by the Miro1-TRAK2 association. **d** Axonal mitochondria are transported by both kinesin-1 and the dynein–dynactin complex, which are recruited to mitochondria predominantly by the Miro1-TRAK1 complex. **e** Syntabulin is an adaptor protein which recruits kinesin-1 to axonal mitochondria. **f** MFN1 recruits TRAK proteins to regulate mitochondrial transport on microtubules. **g** Syntaphilin anchors axonal mitochondria to microtubules in response to elevated Ca^{2+}-levels by inhibiting kinesin-1 activity. **h** Increased glucose levels inhibit kinesin-1-dependent mitochondrial transport in neurons due to the activity of O-GlcNAc transferase on TRAK proteins. **i** Neurofilament and vimentin are the intermediate filaments involved in anchoring and organising mitochondria in neurons

syntaphilin in these demyelinated neurons increases the likelihood of axonal degeneration [155]. Several non-neuronal tissues express a shorter syntaphilin isoform, called short-syntaphilin (S-SNPH), which localises to mitochondria. Hypoxic stress lowers S-SNPH levels in some cancer cell lines which increases their invasiveness due to abrogation of docking and enhanced mitochondrial trafficking to the cell periphery [156].

Microtubule-dependent mitochondrial organisation is determined by post-translational modifications of tubulin, and microtubule-associated proteins

Microtubule stability, governed by MAPs and post-translational modifications (PTMs) of tubulin, impacts mitochondrial transport and distribution. Other molecules including glucose and cytoskeleton interactors such as ADP-ribosylation factors (ARFs), their activators, and adenomatous polyposis coli (APC), have also been reported to mediate mitochondrial transport by interacting with mitochondrial trafficking complexes [97, 157, 158]. However, in most reported instances, the precise mechanism of transport regulation is yet to be uncovered.

Cortisol-mediated destabilisation of microtubules reduces mitochondrial localisation at the cell periphery though detachment of kinesin-1 from microtubules [159]. MAP7 family members not only stabilise microtubules and recruit kinesin-1 to microtubules in vitro, but are also sufficient to enable kinesin-1-dependent mitochondrial transport in the cell [160, 161]. Stable expression of the longest isoform of human tau, a neuronal, microtubule-stabilising protein, leads to aggregations of mitochondria near the MTOC and reduced mitochondrial transport to the cell periphery [162]. Parkin, an E3 ubiquitin ligase which promotes tubulin degradation and mitophagy, is also a MAP which binds to and stabilises microtubules [163, 164]. Mitochondrial transport is perturbed in the absence of Parkin, and is rescued by treatment with microtubule-stabilising drugs [165].

Mitochondrial transport is additionally affected by mutations and PTMs of tubulin. Motor binding to microtubules is impaired and mitochondrial transport is reduced in cells expressing mutant TUB4A isoforms associated with disorders of the nervous system [166]. Tubulin nitration in microtubules arrests anterograde mitochondrial transport [167]. Hyperglutamylation of tubulin upon loss of cytosolic carboxypeptidase 1 (CCP1) reduces microtubule stability and axonal mitochondrial motility in mice [168]. Other studies found that in the absence of CCP1 or both CCP1 and CCP6, neurons display a ~ 50% reduction in the motile mitochondrial population [169, 170]. Thus, polyglutamylation of tubulin correlates with mitochondrial halting on microtubule tracks.

The ARF family of GTPases is known to regulate vesicular trafficking, phospholipid metabolism, and modulate actin dynamics in the cell [171]. ARF-activators maintain mitochondrial distribution by associating with Miro proteins or by limiting the Miro-TRAK association to inhibit dynein–driven mitochondrial transport towards the MTOC [157, 158]. APC stabilises microtubules and is required for a variety of cellular processes such as spindle formation, cellular migration and chromosome segregation [172]. Cancer-associated mutations hamper the ability of APC to bind to the Miro1/TRAK-2 complex, and reduce the frequency of initiation of anterograde mitochondrial transport [97].

Finally, glucose, a crucial nutrient for ATP generation in cells can dictate mitochondrial organisation. Glucose levels regulate synaptic activity and PTMs of the mitochondrial transport machinery, which in turn affect mitochondrial localisation by reducing motility [173, 174]. Glucose levels also regulate the activity of the enzyme O-GlcNAc transferase (OGT) [174]. O-glycosylation of Milton, induced by overexpression of OGT or increased extracellular glucose levels, inhibits bidirectional mitochondrial motility [173]. Furthermore, TRAK1 and TRAK2 are targets of nucleocytoplasmic OGT, which forms a ternary complex with KIF5C and either TRAK [175, 176]. This complex partially limits KIF5C-TRAK1/2-mediated mitochondrial redistribution to the cell periphery [176] (Fig. 4h).

Since microtubules serve as the tracks for a bulk of mitochondrial transport in the cell, it is not unexpected that that microtubule stability impacts mitochondrial transport. To reiterate, destabilisation of microtubules increases mitochondrial fission in *S. pombe*, mitochondrial fission and fusion proteins are involved in tethering mitochondria to other organelles in the cell, and mitochondrial fusion proteins too regulate mitochondrial transport [17, 27, 147, 177, 178]. These results suggest a close nexus between mitochondrial organisation and dynamics, and the microtubule cytoskeleton, with more diverse functions exhibited by the mitochondrial proteins than suggested by current research. In neurons, shorter mitochondria have been observed to be more motile than longer mitochondria [148, 179]. The close association between the mitochondrial fission/fusion proteins and microtubule-based transport is likely a regulatory mechanism that primes mitochondria for effective delivery to destinations within the cell.

Mitochondrial positioning in muscle cells and neurons is mediated by intermediate filaments and associated proteins

Mitochondria associate with the IFs desmin and vimentin, and the linker protein plectin [64, 73]. Desmin is present at sarcoplasmic reticulum-mitochondria-associated membranes and interacts with several mitochondrial proteins in muscle cells [180]. In the absence of desmin, mitochondria are clumped and disorganised [65, 180]. Depletion or mutations of desmin and desmin-binding proteins plectin and myotubularin are accompanied with aberrant mitochondrial organisation, which results in muscle-degeneration [65, 73, 180–184]. Keratin-19 is another IF which promotes proper mitochondrial organisation in muscle cells [67].

Neuronal organisation of mitochondria is dependent on their interactions with IFs vimentin, neurofilament light and associated proteins (Fig. 4i). Vimentin phosphorylation

regulates anchorage of mitochondria to these filaments [66, 185, 186]. Vimentin expression, controlled by microRNA-124, regulates mitochondrial localisation and motility in neurons [187]. Complete loss of the IF neurofilament light increases neuronal mitochondrial motility [188, 189]. While, disease linked aggregations of IFs caused due to mutations in neuronal IFs or associated proteins reduce mitochondrial motility [188, 190]. Thus, intermediate filaments anchor mitochondria either by direct interaction or via IF-associated proteins to regulate intracellular mitochondrial organisation.

Mitochondrial function is modulated by the cytoskeleton

The effect of cytoskeletal organisation on mitochondrial dynamics and organisation influences mitochondrial function and thereby impacts cellular health. Based on changes in the cellular milieu, the cytoskeleton and associated proteins position mitochondria at regions where their function is required. Although the interactions of the cytoskeleton with mitochondria have been found to alter mitochondrial function, the molecular mechanisms underlying this phenomenon are largely unknown [191]. In other words, studies that have investigated the effect of cytoskeletal changes on mitochondrial function have gathered correlative evidence. The cytoskeleton influences mitochondrial quality control and turnover, ATP production and calcium homeostasis [192]. These effects have been particularly evident in cells with high energy demands such as neurons and cardiomyocytes, as detailed below. These changes may be caused by the alteration in mitochondrial fission–fusion dynamics, which is caused by the assembly and disassembly of cytoskeletal proteins. Further studies are required to establish the mechanisms that cause these functional changes.

Mitochondrial membrane potential and ROS production are regulated by F-actin

Abrogation of F-actin depolymerisation in budding yeast results in reduced mitochondrial membrane potential, increased ROS production and reduced lifespan, all of which are hallmarks of apoptosis initiated by mitochondria [49, 50]. On the contrary, a mutation which increases F-actin depolymerisation decreases ROS production and thereby increases the mother-cell-specific lifespan of yeast cells [51]. F-actin depolymerisation induced by oxidative stress leads to mitochondrial fission and thereby causes ischemia reperfusion injury in endothelial cells [193].

In neurons, axonal branching is prevented upon inhibition of cellular respiration, but proceeds at regions enriched with stationary mitochondria in the presence of NGF [194]. F-actin-mediated stalling of mitochondria and translational machinery in specific regions of sensory axons leads to ATP production, and consequently local translation of axonal mRNA to synthesize proteins required for axonal guidance [192, 194]. Inhibition of polymerisation of actin associated with mitochondria isolated from mouse brain increases mitochondrial oxygen consumption rate and cytochrome c oxidase activity [195].

Taken together, perturbation of F-actin dynamics increases the production of mitochondrial ROS and thereby induces oxidative stress in cells.

Microtubules and associated proteins alter mitochondrial function

Stationary mitochondria form local sources of ATP, which are critical for various neuronal functions including local protein translation, axonal branching, synaptic transmission, and driving sodium/potassium pump activity [192, 196].

Clusters of mitochondria positioned by microtubules or F-actin provide energy for local protein translation in dendrites during synaptic plasticity [33, 192]. This could affect the memory of an individual because modification of proteins synthesized by local translation during synaptic plasticity drives memory formation [33]. Mitochondria transported along microtubules and immobilised in the axons by F-actin also play a critical role in the translation of nuclear-encoded mitochondrial mRNAs (mtRNAs), with dysfunctional axonal translation triggering neurodegeneration [197]. It has been proposed that mtRNAs hitchhike on moving mitochondria for subcellular trafficking and arrive at stationary mitochondria, where they are translated [198, 199].

In cardiomyocytes, a change in the microtubule arrangement alters mitochondrial organisation, and leads to defects in calcium release upon nanomechanical stimulus [150]. Destabilisation of microtubules by aberrant phosphorylation of MAP4 leads to mitochondrial dysfunction and apoptosis [200–202]. Hypoxia induces the phosphorylation of three key serine residues of MAP4, which leads to its dissociation from tubulin and translocation to mitochondria [203–205]. This in turn results in the opening of mitochondrial permeability transition pore (mPTP), mitochondrial dysfunction and apoptosis [200]. Inhibition of MTUS1 in endothelial cells also increases mitochondrial ROS production [93].

Tubulin interacts with VDAC to regulate channel permeability and thereby control cellular respiration in muscle cells [206]. Dimeric tubulin increases the voltage sensitivity of VDAC in vitro at physiological salt conditions and regulates membrane permeability, limiting the ATP/ADP flux of mitochondria [206]. It has also been hypothesized that the tubulin-VDAC interaction is the molecular basis

for chemotherapy-induced peripheral neuropathy [207]. In Duchenne muscular dystrophy, low expression of dystrophin, a cytoskeletal protein that binds to tubulin, leads to increased ROS production and reduced mitochondrial Ca^{2+} levels and thereby affects the ETC in mitochondria [208–210].

In all, microtubule destabilisation blocks mitochondrial transport and thereby hampers local protein translation in neurons, which could lead to neurodegeneration. It also possibly induces apoptosis in cardiac muscles and degeneration of skeletal muscles by bringing about mitochondrial defects.

Mitochondrial function and lipid composition are determined by IFs

Several reports indicate that IFs alter mitochondrial positioning and function, particularly in muscle cells [211]. Maximal respiration rates are significantly reduced in the mitochondria of cardiac and soleus muscles of desmin-null mice in situ [65]. Cardiac muscle architecture is severely disrupted, causing muscle degeneration, necrosis and calcification of myocardium in these mice [212]. This results in the development of cardiomyocyte hypertrophy and heart failure, which are also characterised by mitochondrial defects [213, 214].

Physical association of mitochondria with vimentin IFs increases mitochondrial membrane potential [66]. Vimentin also reduces the sensitivity of mitochondria to oxidative stress by preventing the formation of mPTP [215]. This is possibly because vimentin interacts with OMM-localised mPTP regulators [215].

Keratin IFs regulate lipid composition in mitochondria, which leads to increased oxygen consumption and ATP production. In keratinocytes lacking type I Keratin (Krt9 through Krt20), expression of proteins belonging to respiratory complexes I and IV is elevated, and the cardiolipin and phosphatidylethanolamine content in the mitochondria is increased [68]. Krt6 or Krt16 null keratinocytes show increased mitochondrial ROS production, decreased mitochondrial membrane potential and reduced mitochondrial respiration [69]. Mutations in Krt6, Krt16 or Krt17 perturb mitochondrial quality control including mitophagy and lysosomal degradation [216].

The cytoskeleton-associated protein plectin also influences mitochondrial function. Loss of plectin leads to degeneration of striated muscles like cardiac and soleus muscles [72]. Cardiac and skeletal muscle cells devoid of plectin isoforms P1b or P1d alter permeability of the OMM, which is evidenced by a decrease in maximal respiration rate [72].

Taken together, mitochondrial association with IFs alters mitochondrial membrane potential, oxygen consumption rate and energy production.

Future perspectives

In summary, the cytoskeleton and associated proteins play a crucial role in regulating mitochondrial dynamics, organisation, and function. While cytoskeletal interactions with mitochondria are well-characterised, the molecular mechanisms underlying these interactions remain elusive in several cases.

As a number of organelles, namely ER, lysosomes and Golgi-derived vesicles have been implicated in mitochondrial fission, it will be interesting to see how the cytoskeleton-dependent positioning of these organelles is co-ordinated to bring about fission [44, 177, 217]. Mechanical forces have been shown to be sufficient to trigger mitochondrial fission [218]. Therefore, the activity of two opposing families of motor proteins attached to a single mitochondrion might also cause mitochondrial constriction and eventual fission.

The intercellular transport of mitochondria via tunnelling nanotubes is also dependent on the cytoskeleton and is observed in a variety of animal tissue systems, typically as a response to cellular stress [61, 219–222]. However, the mechanisms and the importance of this transport and its regulation are yet to be uncovered.

The cell cycle proceeds with cytoskeletal reorganisation, which in turn affects mitochondrial anchorage [95, 103, 139]. In the few mitochondrial anchors identified thus far, uncovering how these anchors are spatiotemporally regulated in dividing cells, and if those mechanisms are different in post-mitotic cells like neurons, will further our understanding about mitochondrial positioning and the role of the cytoskeleton in this process.

Disruption of the proper form and functioning of the cytoskeleton correlates with severe health implications including muscle degeneration, heart failure and neurodegeneration [223–225]. Changes in mitochondrial morphology, dynamics, motility and function also affect the health of the system [226, 227]. In future, it will be interesting to explore whether a causal relationship exists between cytoskeletal disruption and mitochondrial dysfunction observed in these pathologies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest with the contents of this article.

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