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Review

Mitochondrial inheritance in yeast☆

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ABSTRACT

Mitochondria are the site of oxidative phosphorylation, play a key role in cellular energy metabolism, and are critical for cell survival and proliferation. The propagation of mitochondria during cell division depends on replication and partitioning of mitochondrial DNA, cytoskeleton-dependent mitochondrial transport, intracellular positioning of the organelle, and activities coordinating these processes. Budding yeast *Saccharomyces cerevisiae* has proven to be a valuable model organism to study the mechanisms that drive segregation of the mitochondrial genome and determine mitochondrial partitioning and behavior in an asymmetrically dividing cell. Here, I review past and recent advances that identified key components and cellular pathways contributing to mitochondrial inheritance in yeast. This article is part of a Special Issue entitled: 18th European Bioenergetic Conference. Guest Editors: Manuela Pereira and Miguel Teixeira.

1. Introduction

Most membrane-bounded organelles cannot be made de novo. Rather they grow and multiply from pre-existing organelles and must be inherited upon cell division [1]. Mitochondria are semi-autonomous cell organelles that contain their own genome encoding a small subset of mitochondrial proteins. Growth of mitochondria depends on replication and expression of the mitochondrial genome and import of nuclear-encoded proteins. Multiplication of mitochondria is facilitated by dynamin-related membrane fission proteins, while their appropriate intracellular distribution is ensured by cytoskeleton-dependent transport mechanisms. In sum, these processes are essential for inheritance of mitochondria, maintenance of bioenergetic capacity, and cell survival [2–7].

Nearly half a century has elapsed since the discovery of mitochondrial DNA (mtDNA) [8–10]. However, the molecular and cellular mechanisms of mtDNA inheritance and maintenance remain poorly understood [3,11,12]. Unlike nuclear DNA, the replication and partitioning of mtDNA are not strictly linked to the cell cycle. The mitochondrial genome encodes 13 mitochondrial proteins in humans, 8 in budding yeast, and 2 rRNAs and several tRNAs [3,13]. As these gene products include some of the core subunits of the respiratory chain complexes they are indispensable for the biogenesis of respiratory-competent mitochondria. An intact respiratory chain is essential for life in metazoan animals and humans. Thus, it is not surprising that several maternally inherited diseases are associated with mutations in the mitochondrial genome [14,15]. In addition, even healthy born individuals inevitably suffer from an accumulation of mitochondrial mutations during aging. The respiratory chain produces reactive oxygen species (ROS) as byproducts of ATP production during oxidative phosphorylation. As mitochondria are a major source for ROS, mtDNA is particularly vulnerable to ROS-induced mutations and lesions. As a consequence, gradual and progressive accumulation of mtDNA mutations leads to a loss of functional respiratory chain complexes, resulting in a decline of bioenergetic capacity and eventually age-associated pathologies and death [16]. Thus, inheritance of functional mitochondria requires replication and partitioning of the mitochondrial genome together with selection mechanisms that ensure that intact mtDNA molecules are passed on to the next generation.

The cytoskeleton is essential for intracellular positioning of mitochondria, for their ordered inheritance upon cytokinesis, and for maintenance of mitochondrial tubular shape. Depending on the organism and cell type, mitochondria interact with different cytoskeletal elements. In animal tissues, microtubule-dependent long-distance transport of mitochondria is of major importance, while actin filaments are required for local organellar movements [6,17,18]. Myosin-driven actin-dependent transport of mitochondria was described in several metazoans and higher plants. For example, Myo19 is expressed in multiple tissues of vertebrates, localizes to mitochondria and functions in actin-based mitochondrial motility [19], and plant class XI myosins colocalize with mitochondria in maize [20] and mediate mitochondrial trafficking in leaf cells of tobacco [21,22]. In fungi, the use of cytoskeletal tracks for mitochondrial movement is surprisingly diverse: Mitochondrial movement depends on microtubules in fission yeast *Schizosaccharomyces pombe* [23] and in the filamentous fungus *Neurospora crassa* [24,25], whereas mitochondria move along actin filaments in *Saccharomyces*

Abbreviations: ERMES, ER mitochondria encounter structure; MECA, mitochondria–ER–cortex anchor; mtDNA, mitochondrial DNA; ROS, reactive oxygen species

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cerevisiae [26] and in the filamentous fungus *Aspergillus nidulans* [27]. These cytoskeleton-mediated transport processes are crucial for mitochondrial inheritance during cell division.

Budding yeast *S. cerevisiae* has been used extensively to study the molecular machinery and cellular pathways that contribute to mitochondrial inheritance [12,28–30]. In this review, I highlight past and recent advances that lead to an understanding of mitochondrial inheritance in yeast as a simple eukaryotic model organism.

2. Maintenance of mtDNA

S. cerevisiae is an excellent model organism to genetically dissect the cellular and biochemical pathways required for maintenance of respiratory activity, because it is capable of satisfying its energy requirements with ATP generated by fermentation [31–33]. Thus, oxidative phosphorylation and the presence of the mitochondrial genome are dispensable as long as fermentable carbon sources, such as glucose, are present in the growth medium. Even when oxygen is available, yeast cells generate ATP primarily by glycolysis with ethanol as an end product of fermentation. However, when yeast cells are grown on non-fermentable carbon sources, such as glycerol or ethanol, respiration and the presence of an intact mitochondrial genome become essential. Mutants defective in oxidative phosphorylation form small colonies on media containing limiting amounts of fermentable carbon sources. The term *petite* has been coined to describe this characteristic phenotype [34]. Respiratory-deficient strains carrying mutations in the nuclear genome are referred to as nuclear *petite* or *pet* mutants, whereas mutants with lesions in the mitochondrial genome are referred to as cytoplasmic *petite*. Cytoplasmic *petite* mutants that have long deletions in the mitochondrial genome are termed [rho^-], mutants completely lacking mtDNA are termed [rho^0], and cells containing a functional mitochondrial genome are termed [rho^+] [35].

Most of the mtDNA in *S. cerevisiae* is present as linear molecules of variable length. It is thought that few circular mtDNA molecules serve as templates for amplification by a rolling circle mechanism forming concatemers composed of linear arrays of several genome units [10,36,37]. Some of the key components required for propagation of mtDNA have been identified and characterized (Table 1). Mip1, the ortholog of human DNA polymerase gamma (POLG), is the mitochondrial DNA polymerase in yeast [38]. In contrast to metazoans, where the mitochondrial DNA polymerase consists of a catalytic and two accessory subunits, yeast Mip1 is a single chain enzyme [39]. At least three proteins contribute to mtDNA partitioning by promoting recombination: Mhr1, a protein involved in homologous recombination in mitochondria [40], Cce1, a mitochondrial cruciform cutting endonuclease [41,42], and Ntg1, a base excision repair enzyme [43]. Intriguingly, the activity of Mhr1 and Ntg1 is also required for repair of oxidatively damaged mtDNA [44–46]. Further proteins directly involved in mtDNA metabolism include Hmi1 and Pif1, two mitochondrial DNA helicases [47,48], and Apn1, a DNA repair protein active in the nucleus and mitochondria [49]. For yet unknown reasons maintenance of mtDNA in yeast depends on the integrity of the mitochondrial translation machinery [50–52].

It is still a matter of debate whether the mitochondrial RNA polymerase, Rpo41, plays a direct role in maintenance of mtDNA [52]. The mitochondrial genome contains several origins of replication. It is assumed that these *ori* sites represent transcription start sites recognized by Rpo41, and that transcripts are then further processed to produce primers for replication [39]. However, Rpo41-independent DNA replication mechanisms clearly exist, as some [rho^-] mitochondrial genomes can be stably maintained in Δ*rpo41* null mutants [53,54]. In sum, it appears that mtDNA replication in yeast, at least in some cases, is initiated by transcription at *ori* sites and proceeds by a rolling circle mechanism that is initiated through homologous recombination. It is currently not clear to what extent different pathways of mtDNA replication initiation overlap or complement each other.

The mitochondrial genome is packaged into protein–DNA complexes. These structures are called nucleoids by analogy to DNA-organizing structures in bacteria, even though mtDNA packaging proteins probably are of eukaryotic origin [55]. *S. cerevisiae* has about 10–40 nucleoids per cell which are anchored to the mitochondrial inner membrane and evenly spaced along the mitochondrial reticulum (Fig. 1). Each nucleoid contains several mtDNA copies [3,12,52,55]. The major DNA-binding protein of yeast nucleoids is the non-histone high mobility group protein Abf2 [56]. Abf2 plays a major role in packaging of mtDNA, protects it against nuclease attack and chemical damage, and binds and stabilizes recombination intermediates [57–59]. Additional nucleoid components are the proteins required for DNA replication, transcription, repair, and recombination [55]. Other proteins that were found in nucleoids include the mitochondrial chaperonin Hsp60, which was proposed to be required for nucleoid division [60], the citric acid cycle enzyme aconitase, which was suggested to couple mtDNA maintenance with cell metabolism [61], and various other heat shock proteins, metabolic enzymes, and proteins of unknown function [3,55].

Surprisingly little is known about the cellular mechanisms of mtDNA segregation in yeast cells. During its sexual life cycle two haploid yeast cells of opposite mating type fuse to form a diploid zygote. If the parental cells contribute different mitochondrial genomes the zygote contains a mixture of mtDNAs with different genotypes, a state termed heteroplasmy. However, within few cell divisions the mtDNAs unmix, and cells become homoplasmic [3,62]. Genetic evidence suggests that only a small fraction of the mtDNA pool is transferred from the zygote to the bud, and that the position of the bud determines which parental cell contributes its mtDNA. Cells that bud from the mid-point of the zygote inherit mtDNA from both parents, whereas those that bud from either end preferentially inherit mtDNA from only one parent [3,63]. Furthermore, examination of fluorescently labeled nucleoids in zygotes indicated that nucleoids are anchored within the organelle and remain localized in distinct parts of the cell [64,65]. Thus, it is thought that diffusion of mtDNA within the organelle is limited. Instead, it is actively transported into the bud by a yet poorly characterized nucleoid segregation apparatus [3,66]. Presumably, similar mtDNA segregation mechanisms are active in zygotes and vegetatively growing cells.

3. Bud-directed mitochondrial transport

S. cerevisiae has been used extensively to study the molecular mechanisms of organelle inheritance [28,29,67–69]. During mitotic growth yeast cells multiply by asymmetric cell division, a process termed budding. At the beginning of each cell cycle cells become polarized and select a site for bud emergence. Growth is initially restricted to the bud tip and then switches to even expansion over the entire bud surface. As the bud reaches the size of the mother cell, growth is directed to the bud neck, and a septum is formed that separates the daughter cell from its mother. Correct organelle partitioning is achieved by active and directed transport of organelles to the growing bud concomitant with retention of a portion of the organelles in the mother cell [69]. Actin cables that consist of bundles of actin filaments provide the tracks for directed transport processes during cell growth. These cables are assembled by formins, conserved proteins that are located at the bud tip or bud neck and associate with the plus ends of actin filaments. Thus, polarized actin cables initially extend from the growing bud deep into the mother cell. When the bud grows larger formins are relocated from the bud tip to the bud neck and assemble cables that emanate from the bud neck and extend into the mother and daughter [69,70].

Immediately after bud emergence mitochondria enter the bud to ensure inheritance of the organelle (Fig. 1). Mounting evidence suggests that bud-directed mitochondrial movement along actin cables is driven by myosin motor proteins. Already in 1994 an ATP-sensitive, reversible actin-binding activity was detected on isolated yeast mitochondria [71]. As this interaction displayed all characteristics of actin–myosin interactions and could be blocked by pretreatment of actin filaments with

Table 1
Key proteins of mitochondrial inheritance and partitioning in budding yeast.

Protein (alternative name)	Proposed function	Mutant phenotype related to mitochondrial inheritance	Key references
mtDNA metabolism			
Abf2	mtDNA packaging	Increased petite frequency	[56]
Aco1	Aconitase, additional role in mtDNA maintenance	Loss of mtDNA	[61]
Apn1	Endonuclease	Loss of mtDNA	[49,51]
Cce1 (Mgt1)	mtDNA recombination	Increased petite frequency	[41,42]
Hmi1	Mitochondrial DNA helicase	Loss of mtDNA	[47,51]
Mhr1	mtDNA recombination	Increased petite frequency	[40,44]
Mip1	mtDNA replication	Loss of mtDNA	[38]
Ntg1	Endonuclease	?	[43,45]
Pif1	Mitochondrial DNA helicase	Loss of mtDNA	[48,51]
Rpo41	Mitochondrial transcription	Respiratory deficiency	[39]
Bud-directed transport			
Mmr1	Myo2 recruitment to mitochondria	Mitochondrial accumulation in the mother	[79,83]
Myo2	Mitochondrial motor	Impaired anterograde mitochondrial transport	[73,81–83]
Ypt11	Myo2 recruitment to mitochondria	Delayed mitochondrial transport to the bud	[73,90]
Mitochondrial partitioning			
Mdm36	Mitochondrial cell cortex anchor in the mother	Increased mitochondrial motility	[111,112]
Mmr1	Mitochondrial bud tip anchor	Mitochondrial accumulation in the mother	[105]
Num1	Mitochondrial cell cortex anchor in the mother	Increased mitochondrial motility	[106,110,112]
Mitochondrial morphology and dynamics			
Dnm1	Mitochondrial fission	Interconnected mitochondria	[129]
Fcj1	Formation of cristae	Increased frequency of misshapen nucleoids	[129]
Fzo1	Mitochondrial fusion	Loss of mtDNA	[114,115]
Mdm10	ERMES component, mtDNA partitioning	Impaired mitochondrial motility, unstable mtDNA	[120,126]
Mdm12	ERMES component, mtDNA partitioning	Impaired mitochondrial motility, unstable mtDNA	[122,126]
Mdm31	Maintenance of mtDNA	Impaired mitochondrial motility, unstable mtDNA	[125]
Mdm32	Maintenance of mtDNA	Impaired mitochondrial motility, unstable mtDNA	[125]
Mdm34 (Mmm2)	ERMES component, mtDNA partitioning	Impaired mitochondrial motility, unstable mtDNA	[121,126]
Mmm1	ERMES component, mtDNA partitioning	Impaired mitochondrial motility, unstable mtDNA	[123,124,126]
Mos1 (Mio10, Mcs10)	Formation of cristae	Increased frequency of misshapen nucleoids	[129]

myosin heads it was proposed that mitochondria–actin interactions are mediated by a myosin motor protein [71]. This assumption was further supported by the development of a mitochondria-driven microfilament gliding assay that revealed a motor activity on the mitochondrial surface [72]. However, the identification of the motor protein was complicated by the fact that two of the five yeast myosins are encoded by essential genes impeding a straight-forward analysis of deletion mutants [72]. The isolation of mutant myosin alleles with a specific mitochondrial phenotype was later achieved by analysis of the genetic interactions of *YPT11*, encoding a rab-type small GTPase, with *MYO2* [73]. The essential *MYO2* gene encodes a class V myosin that was previously shown to function in anterograde transport of secretory vesicles, vacuoles, peroxisomes, and late Golgi cisternae [69,74–76]. As class V myosins are processive molecular motors transporting various membrane-bounded organelles towards the plus ends of actin filaments [77,78], Myo2 is an obvious candidate for a mitochondrial motor. Consistent with the observation that certain conditional *myo2* mutants show defects in mitochondrial distribution towards the bud [73,79–83] cells depleted of Myo2 or its essential light chain, Mlc1, contain abnormal mitochondria [81,84]. Furthermore, isolated mitochondria lacking functional Myo2 lose their ability to interact with actin filaments in vitro [81]. Taken together, these observations suggest that Myo2 drives anterograde mitochondrial movements in budding yeast.

Myo2 is recruited to its cargo organelles by binding to specific receptors in the organellar membranes. Mmr1 is a protein of the mitochondrial outer membrane and physically interacts with the cargo binding domain of Myo2 [79,85]. Overexpression rescues the mitochondrial transport defects of certain *myo2* mutants and promotes mitochondrial accumulation in the bud [79,83,86]. Thus, it has been suggested that Mmr1 functions as a mitochondrial cargo adapter protein for Myo2 [79,83,85]. While it remains possible that Mmr1 participates in this process it appears unlikely that it is sufficient to recruit Myo2 to

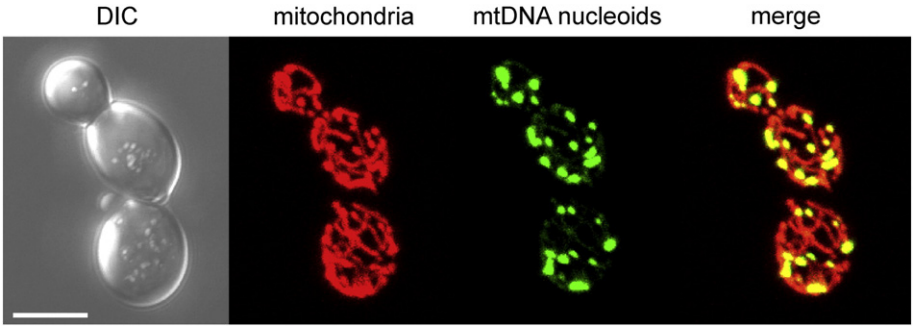

Fig. 1. Mitochondria and mtDNA nucleoids in yeast. Wild type yeast cells expressing mitochondria targeted ERFP [141] and Abf2-GFP [125] were grown to the logarithmic growth phase in minimal medium containing fermentable carbon sources and analyzed by differential interference contrast (DIC) and 3D confocal microscopy. The image shows two cells in different cell cycle stages, one cell carrying a large bud and another cell carrying a small bud. Fluorescence images are maximum intensity projections of red (mitochondria), green (mtDNA nucleoids), and merged z-stacks. Bar, 5 μm. Images are courtesy of Dirk Scholz.

mitochondria. Several *myo2* mutants with mutations in the cargo binding domain show severe mitochondrial distribution defects, and genetic evidence suggests that Myo2-dependent mitochondrial transport is a process essential for cell viability [82,83]. If Mmr1 would constitute the mitochondrial Myo2 receptor, similarly severe phenotypes would be expected for Δ*mmr1* mutants. However, Δ*mmr1* mutants have a rather mild mitochondrial distribution and inheritance defect [79] and are viable both on fermentable and non-fermentable carbon sources [51]. A recent genetic analysis indicates that either Mmr1 or Ypt11 are required to recruit Myo2 to mitochondria. Inheritance is blocked only when both components are mutated at the same time suggesting that they might have redundant functions [83]. It remains a challenge for the future to find out whether additional proteins exist that constitute the mitochondrial Myo2 receptor and play an essential role in mitochondrial inheritance.

Targeting of myosin V motors to their cargo is often supported by rab-type GTPases [87,88]. In yeast, Ypt11 was shown to interact with Myo2 in mitochondrial inheritance [73,82,83,86] and bud-directed transport of the Golgi [89]. Its presence on mitochondria is required for efficient mitochondrial inheritance [90], presumably by recruitment of Myo2 [82,83,90]. Intriguingly, Ypt11 activity is controlled by phosphorylation and degradation [90]. As the ratio of mitochondrial content in the mother and daughter cell depends on Ypt11 [91] it appears likely that tuned Ypt11 activity provides the cell with a means to regulate mitochondrial abundance in the bud.

An alternative motility model suggests that mitochondria are moved by a motor-independent mechanism that uses forces generated by actin polymerization and dynamics [18,92,93], similar to the movement of early endosomes or bacterial pathogens such as *Listeria monocytogenes*. According to this model, two members of the Puf family of RNA-binding proteins, Jsn1 and Puf3, recruit the Arp2/3 complex, the cell's most important initiator of actin polymerization, to the mitochondrial surface [94,95]. Forces generated by actin polymerization might then drive mitochondrial movement [93]. A complex composed of three proteins essential for mitochondrial distribution and morphology, Mdm10, Mdm12 and Mmm1, was proposed to link mitochondria to their cytoskeletal tracks and provide directionality to Arp2/3-dependent movement. This complex was termed “mitochore” as it was suggested to function in mitochondrial inheritance in a similar manner as the kinetochore in mitosis [96]. In this scenario the role of Myo2 in mitochondrial transport would be only indirect and accumulation of mitochondria in the mother cells of *myo2* and *ypt11* mutants is predicted to be caused by defects in retention of mitochondria at the bud tip [18,80,92].

Is the main driving force for bud-directed mitochondrial movement provided by Myo2 or by a motor-independent mechanism? Several years after proposal of the “mitochore” model it turned out that Mmm1 in fact is an ER protein [97] rather than a mitochondrial outer membrane protein, as it was originally published [98]. The ER localization of Mmm1 is not compatible with its proposed “mitochore” function, and its function in mitochondrial inheritance will be discussed below. Intriguingly, mitochondrial inheritance defects in *myo2* mutants can be rescued by expression of a chimeric mitochondria-specific motor, Myo2-Fis1, that carries a mitochondrial outer membrane anchor in place of the cargo binding domain [82]. This rescue would not be expected if the main function of Myo2 in mitochondrial inheritance would be merely transport of a retention factor. Furthermore, mitochondria-specific loss-of-function alleles of *myo2* are synthetic lethal with Δ*ypt11* and can be rescued by Myo2-Fis1. This is genetic evidence for an essential and direct role of Myo2 in anterograde mitochondrial transport [82,83]. Last but not least, Myo2 was detected on the surface of isolated mitochondria by immunoelectron microscopy [82]. Taken together, these data suggest that Myo2 is the main mediator of anterograde mitochondrial movement in yeast, and that its activity is supported by Ypt11 and Mmr1 (Table 1). While Arp2/3-dependent actin polymerization clearly cannot compensate a loss of Myo2 function it is still possible that motor-independent mechanisms contribute to mitochondrial motility, e.g. by random short distance movements that can be observed in *myo2* mutants.

4. Mitochondrial partitioning

Yeast mitochondria are highly dynamic cell organelles that continuously move back and forth along cytoskeletal tracks and frequently fuse and divide [29,99,100]. Partitioning of mitochondria between the mother cell and the bud is ensured by concerted action of anterograde and retrograde movements together with attachments of mitochondria to the cell cortex. Parts of the mitochondrial network appear to be fixed at the tip of the growing bud and at the opposite pole of the mother cell. These retention zones are thought to contribute to equal distribution of mitochondria among mother and daughter cells before cytokinesis [101–103].

Only little is known about the mechanisms of retrograde mitochondrial transport. It is thought that the organelles are attached to actin cables that extend into the mother cell, and that formin-induced retrograde flow of these cables moves the mitochondria away from the bud [92,101]. However, proteins that are specifically involved in this process have not been identified.

Recent research suggests that distinct protein complexes anchor mitochondria at the bud tip and in the mother cell (Table 1). Mmr1 is an obvious candidate for a factor mediating attachment of mitochondria in the bud as its mRNA is specifically localized to buds [104] and the protein is highly enriched in bud-localized mitochondria [79]. Mmr1 was localized by super-resolution microscopy to mitochondrial ER contact sites in the bud. Thus, it appears that Mmr1 provides a mitochondrial ER anchor preventing backwards movement of newly inherited mitochondria [105]. Consistent with such a function mitochondrial content is decreased in buds of cells lacking Mmr1, and mitochondria accumulate in the mother cell of Δ*mmr1* mutants [79,105,106]. The interaction partners of Mmr1 in the ER membrane are currently unknown. Further work will be required to find out whether the main function of Mmr1 is recruitment of Myo2 to mitochondria or attachment of mitochondria to bud-localized ER. It is also possible that both activities are related or that Mmr1 has dual functions.

Num1 is a cell cortex-associated protein that preferentially localizes to mother cells and can be found in buds only late during the cell cycle [107,108]. It interacts with dynein and microtubules and facilitates migration of the nucleus from the mother cell to the emerging bud [109]. Unexpectedly, it was found that a subfraction of the mitochondrial division protein Dnm1 forms complexes with Num1. Intriguingly, double mutants lacking both Num1 and Dnm1 frequently show mother cells devoid of mitochondria while mitochondria accumulate in the bud. Based on this observation it was suggested that Num1 could play a role in retention of mitochondria in the mother [110]. Several lines of recent evidence support this hypothesis. First, mitochondria in Δ*num1* null mutants display an increased motility suggesting that anchors immobilizing mitochondria are lacking [106,111]. Second, Num1 forms punctate structures at the cell cortex that colocalize with the ends of mitochondrial tubules and presumably represent these anchors [106,112]. And third, synthetic mitochondria–plasma membrane tethers rescue mitochondrial defects in Δ*num1* mutants demonstrating that its function as a cortex tether is important for mitochondrial inheritance [106,112]. Intriguingly, Δ*num1* and Δ*mmr1* deletion mutants show positive genetic interactions suggesting that both proteins execute antagonistic functions [113]. Consistent with this observation deletion of the *NUM1* gene rescues the mitochondrial inheritance defect in Δ*mmr1* mutants [106]. Thus, it appears that Mmr1 promotes inheritance of mitochondria to the bud while Num1 ensures that a portion of mitochondria is retained in the mother cell. The combined activity of both processes controls equal partitioning of mitochondria during cell division.

We are only beginning to understand the molecular mechanisms that lead to the formation of Num1 cortex anchors. Purification and mass spectrometric analysis of the Num1 complex identified Mdm36

as one of its constituents [112]. Mdm36 is a mitochondria-associated protein, and mitochondria of Δ*mdm36* null mutants are highly motile, similar to Δ*num1* mutants [111]. Furthermore, mitochondrial morphology defects of Δ*mdm36* mutants can be rescued by synthetic mitochondria–plasma membrane tethers [106]. These observations suggest that Mdm36 is a mitochondrial receptor mediating binding of Num1 to mitochondria [112]. Interestingly, several ER proteins also copurified with Num1, and Num1-mediated mitochondrial-cortex tethers colocalize with cortical ER. Thus, it was suggested that Num1 is a key component of novel cellular structure termed MECA (mitochondria–ER–cortex anchor) [112]. On the other hand, electron tomography revealed that mitochondria directly contact invaginations of the plasma membrane without participation of the ER [106]. Thus, the role of the ER in mitochondrial anchoring in the mother cell remains ambiguous.

5. Orchestration of mitochondrial dynamics and inheritance

The faithful distribution of mitochondria and mtDNA during cell division depends on multiple pathways, including mitochondrial motility, tethering, fusion and fission, and mtDNA partitioning. How are these processes interlinked and coordinated?

Several components that have a primary function in mitochondrial distribution and morphology also play a role in mtDNA inheritance (Table 1). The shape of the tubular mitochondrial network of vegetatively growing yeast cells is maintained by opposing fusion and fission events [100]. Deletion mutants lacking factors essential for mitochondrial fusion, such as Δ*fzo1* mutants, are unable to inherit mtDNA [114,115]. This mtDNA inheritance defect can be rescued by deletion of genes encoding proteins essential for mitochondrial division, such Dnm1. The mitochondrial compartment of Δ*fzo1* Δ*dnm1* double mutants has an almost wild type-like shape, but is no longer dynamic [116,117]. The fact that double mutant cells are [rho^+] indicates that the tubular shape of mitochondria, rather than their dynamic behavior, is essential for mtDNA inheritance.

The ERMES complex (ER mitochondria encounter structure) consists of two integral mitochondrial outer membrane proteins, Mdm10 and Mdm34, one mitochondria-associated soluble protein, Mdm12, and one integral ER protein, Mmm1. It constitutes a physical ER–mitochondria tether and is thought to be involved in the exchange of lipids between the two organelles [97,118]. In addition, one ERMES subunit, Mdm10, has been shown to assemble also into the SAM complex which mediates sorting and assembly of β-barrel proteins in the mitochondrial outer membrane [119]. Mutants lacking either one of the ERMES subunits typically contain large, swollen mitochondria, frequently carry buds devoid of mitochondria, and have a tendency to lose the mitochondrial genome after several generations of growth [98,120–122]. Interestingly, GFP fusions of the ER-localized ERMES subunit Mmm1 were found to be located in small, punctate structures adjacent to a subset of matrix-localized mtDNA nucleoids [123], suggesting that at least some nucleoids are connected to the ER by a complex that spans both mitochondrial membranes. Intriguingly, Mmm1 colocalizes with the mitochondrial nucleoid component Mgm101 even in the absence of mtDNA, and the membrane-spanning structure forms a self-replicating unit that is faithfully inherited into newly formed buds. Furthermore, the nucleoids colocalizing with Mmm1 contain Mip1 and are actively replicating, as shown by incorporation of BrdU into newly synthesized mtDNA in pulse-labeling experiments [124]. Based on these observations it was proposed that ERMES is part of a larger complex that spans both mitochondrial membranes and connects mitochondrial nucleoids to the ER to control mtDNA replication or distribution [118]. Mitochondrial inner membrane proteins participating in this process remain unknown. Possible candidates are two related inner membrane proteins, Mdm31 and Mdm32. Deletion mutants have phenotypes very similar to ERMES mutants, including aberrant nucleoid structure and loss of mtDNA, and deletion of *MDM31* or *MDM32* is synthetic lethal with deletion of genes encoding ERMES subunits [125]. It is tempting to speculate that Mdm31, Mdm32 and ERMES subunits connect mitochondrial nucleoids to an extra-mitochondrial mtDNA segregation machinery [96,124,125]. However, direct evidence for such a function is still lacking, and the forces mediating directed transport of nucleoids are unknown.

A recent study examining the role of mitochondrial ER contacts in mitochondrial division gave a new twist to the role of ERMES in mtDNA distribution and revealed a link of mitochondrial division and mtDNA partitioning [126]. ER tubules wrap around mitochondria and mark mitochondrial division sites. This activity is presumably required to constrict the organelle to allow assembly of the Dnm1 division ring [127,128]. Many mitochondrial division events are spatially linked to the ERMES complex, suggesting that ERMES triggers ER-associated mitochondrial division. Remarkably, also ERMES-linked nucleoids are associated with these sites. These nucleoids often exhibit oscillatory movements and rapidly segregate and re-coalesce prior to mitochondrial division. This results in partitioning of nucleoids to the two newly formed mitochondrial tips thus ensuring that each mitochondrion inherits mtDNA. This mechanism likely contributes to efficient mtDNA distribution throughout the cell [126].

It was recently suggested that also the internal structure and interconnectivity of the mitochondrial network influence the spreading of mtDNA, and that Fcj1 and Mos1 are involved in this process [129]. Fcj1, the ortholog of mammalian mitofilin, and Mos1 (alternative names Mio10 or Mcs10) are components of a multi-subunit complex in the mitochondrial inner membrane. Three different laboratories recently found that this complex is a key determinant of mitochondrial architecture. According to its function it was named MICOS (mitochondrial contact site) [130], MINOS (mitochondrial inner membrane organizing system) [131], or MitOS (mitochondrial organizing structure) [113]. Fcj1 is involved in the formation of mitochondrial cristae [132] and was found to colocalize with nucleoids [129]. Cells lacking Fcj1 or its interaction partner Mos1 contain an increased number of enlarged nucleoids. The fraction of cells containing misshapen nucleoids is further increased upon additional deletion of the *DNM1* gene. Based on these observations a model was proposed suggesting that not only mitochondrial division but also mitochondrial cristae separate nucleoids from each other. When these separating activities are absent, nucleoids may coalesce and can no longer be evenly distributed throughout the mitochondrial network and cells become [rho^0] more rapidly [129].

Mitochondrial dynamics is functionally linked to mitochondrial anchoring in several ways. Strikingly, the presence of Num1 is essential for viability in cells lacking both Dnm1 and Fzo1, and triple mutants carrying Δ*dnm1* and Δ*num1* null alleles in combination with the conditional *fzo1-1* allele frequently show mother cells devoid of mitochondria at the non-permissive temperature [112]. This indicates that retention of mitochondria in the mother becomes essential when the mitochondrial network is not dynamic. Also a Δ*dnm1* Δ*num1* double deletion produces mother cells depleted of mitochondria [110] and is lethal in some genetic backgrounds [133]. Cells lacking Dnm1 contain a single, interconnected mitochondrion. It is conceivable that in mutants lacking Dnm1 anterograde transport mechanisms move the entire mitochondrion into the bud when Num1 anchors in the mother are lacking. This situation causes death to the mother cell as mitochondria are essential organelles. Frequent fusion and fission may counteract this partitioning defect by separating distinct parts from the mitochondrial network to facilitate their transport back into the mother cell by retrograde transport.

Moreover, several studies reported that Δ*num1* and Δ*mdm36* cells have aberrant mitochondria resembling bona fide mitochondrial division mutants [110,111,134]. What is the role of Num1 and Mdm36 in mitochondrial fission? The scission of membranes by dynamin is facilitated by pulling forces that generate longitudinal tension on the membrane [135]. It was proposed that anchoring of mitochondria together with cytoskeleton-dependent forces pulling on the organelle is required to generate tension to help Dnm1 severing the mitochondrial membranes

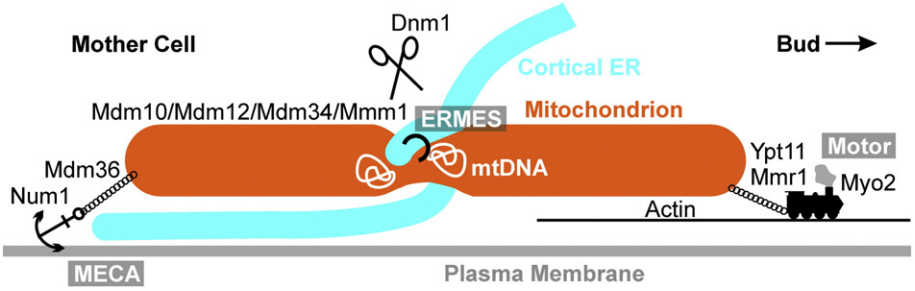

Fig. 2. Model for the orchestration of mitochondrial transport, retention, fission, and mtDNA partitioning in mitochondrial inheritance. The myosin motor, Myo2, together with the rab-type GTPase, Ypt11, and the mitochondrial membrane protein, Mmr1, mediates bud-directed transport of mitochondria along tracks provided by actin cables. This activity is antagonized by Num1-containing cell cortex anchors in the mother cell. Num1 directly interacts with the plasma membrane and is recruited to the mitochondrial surface by Mdm36. The role of the cortical ER in this process and the formation of a mitochondria–ER–cortex anchor (MECA) is not completely understood. The antagonistic activities of Myo2 and Num1 generate tension on the mitochondrial membranes which supports fission by the dynamin-related protein, Dnm1. Mitochondrial fission sites are selected by the ER–mitochondria encounter structure (ERMES) which consists of Mdm10 and Mdm34 in the mitochondrial outer membrane, Mmm1 in the ER membrane, and the soluble protein Mdm12 (here, ERMES is symbolized by an open ring). Division and partitioning of mtDNA nucleoids is coordinated at sites marked by ERMES. See text for further details.

[136]. Indeed, synthetic mitochondrial plasma membrane tethers rescue the mitochondrial fission defect in Δ*num1* and Δ*mdm36* cells indicating that mitochondrial anchoring contributes to mitochondrial fission [106].

In sum it appears that the pathways contributing to mitochondrial inheritance are functionally interlinked in many ways. This holds true for several of the processes discussed above. First, mitochondrial motility and anchoring are antagonistic processes; second, mitochondrial dynamics is important for mtDNA partitioning and inheritance; third, mitochondrial ER contacts contribute to mtDNA partitioning; fourth, mitochondrial division is a prerequisite for mitochondrial segregation; and fifth, mitochondrial cell cortex anchors contribute to mitochondrial fission. A model depicting the interconnections of mitochondrial transport, retention, division, and mtDNA partitioning is shown in Fig. 2. However, we are only beginning to understand the complex interplay of these processes, and several of the molecular components remain to be discovered.

Emerging evidence suggests that mitochondrial partitioning is an important factor during aging. Yeast mother cells produce only a limited number of daughter cells before they die, a phenomenon called replicative life span. It is thought that during asymmetric cell division active and healthy cell components are preferentially transmitted to the bud, whereas damaged components are retained in the mother [137]. Consistent with this model it was reported that a mutation of the *ATP2* gene, encoding a subunit of the mitochondrial F_1 ATP synthase, results in decreased respiratory activity and accumulation of mitochondria in the mother, suggesting that damaged mitochondria are less efficiently transported to the bud [138]. Intriguingly, carbonylated proteins which accumulate during aging are particularly abundant in mitochondria of the mother cell [139]. Furthermore, experiments employing fluorescent biosensors suggest that bud-localized mitochondria produce fewer ROS and are more reducing compared to mother-cell mitochondria [140]. This combined evidence suggests that an age-associated mother–daughter asymmetry exists. Deletion of *MMR1* or *YPT11* causes loss of the mother–daughter age asymmetry [91,140] indicating that mitochondrial transport and retention mechanisms play an important role in yeast replicative aging. However, the molecular mechanisms coupling mitochondrial quality control and inheritance are yet to be determined. Thus, mitochondrial inheritance in yeast will remain an exciting field of research in the coming years.

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