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Integrating mitochondrial organization and dynamics with cellular architecture

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Mitochondrial organization, dynamics, and interactions with other intracellular structures and organelles are crucial for proper cell physiology. In this review we will discuss recent work on the significance of mitochondrial organization in regulating the size and distribution of mitochondrial DNA nucleoids and emphasize the importance of a new role for actin in regulating mitochondrial dynamics. We will also highlight new and unexpected examples of how mitochondria are integrated with many aspects of cell behavior, including cell migration, cell division, and the proper functioning of specialized cells such as neurons and immune cells. Together, these recent studies demonstrate the importance of mitochondrial organization in generating cellular architecture and vice versa.

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Introduction

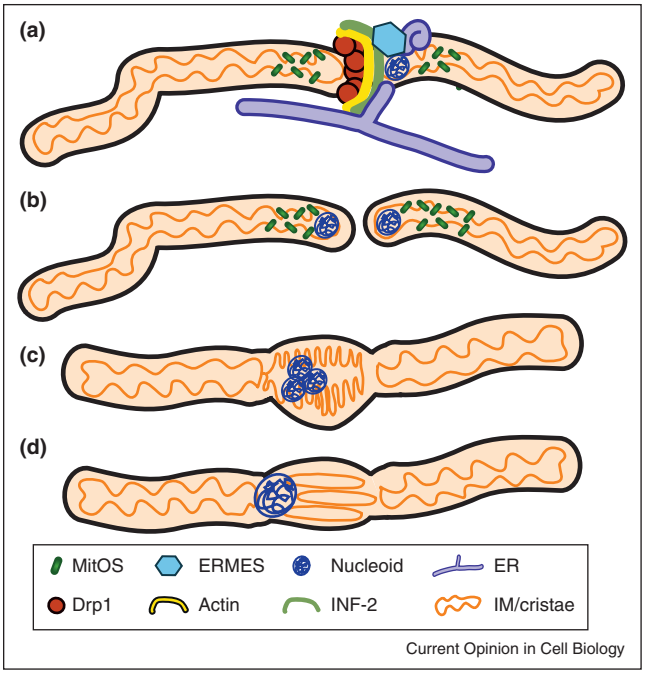
Mitochondria form tubular networks that exhibit a wide range of geometries depending on cell type and environmental conditions. The organization of mitochondrial networks is generated through constant dynamics of tubule fission and fusion, movements along cytoskeletal tracks, and mechanisms that position mitochondria in specific regions of the cell (reviews listed below). Together these mechanisms ensure that mitochondria are distributed throughout the cell, are segregated properly upon cell division, and are at the right place at the right time to provide their essential metabolic and signaling functions. Mitochondria directly interact with other organelles and subcellular structures, such as the endoplasmic reticulum (ER) and the cytoskeleton and these interactions allow mitochondria to both be influenced by, and in turn, contribute to generating cellular architecture. There have been numerous recent reviews documenting how mitochondria are shaped, positioned, and interact with the ER, to which we refer readers for more information [1–6]. In this review we will begin with a focus on the most recent studies of how mitochondrial organization influences mitochondrial DNA (mtDNA) distribution (Figure 1), not covered in these reviews. We will then expand on how mitochondrial organization and dynamics are integrated with internal cellular architecture (Figure 2) by highlighting specific examples in the recent literature.

Organization and distribution of mtDNA

Mitochondria carry their own genome, which encodes proteins required for oxidative phosphorylation (OXPHOS) along with its own rRNAs and tRNAs that are required for translation of these transcripts. The mtDNA is organized into nucleoprotein structures called nucleoids, which are distributed throughout the mitochondrial network. The number of mtDNA copies can vary anywhere from 1 to 10 copies per nucleoid and the number of nucleoids ranges from 10 to 1000 per cell, depending on cell type and organism [7,8]. Nucleoids cannot form de novo and thus their inheritance is essential for mitochondrial respiratory function. Mitochondrial organization and dynamics greatly influence mtDNA maintenance. For example, cells with overfragmented mitochondrial networks, due to decreased levels of mitochondrial fusion, contain decreased amounts of mtDNA or even lose it completely [9–11]. An emerging mechanism to distribute mtDNA throughout the mitochondrial network is the close proximity between mtDNA nucleoids and the sites of mitochondrial fission events observed both in budding yeast and mammalian cells (70–80% of division events occur near nucleoids) (Figure 1a) [12•,13••]. In yeast, most of these division events result in a nucleoid present in each newly generated mitochondrial tubule tip that is generated upon fission (Figure 1b) [13••]. The proximity of nucleoids to fission sites would ensure that a freshly divided mitochondrial tubule, now separated from the network, contains and carries along a nucleoid until re-fusing to another part of the network, thus spreading nucleoids throughout the network through mitochondrial fission and fusion dynamics. If fission is decreased, mtDNA nucleoids are seen to cluster together, grow in size and lose their distribution throughout the mitochondrial network [12•,14,15,16•]. This abnormal mtDNA organization in turn can alter the morphology of the mitochondria themselves, generating thicker, bulging regions of mitochondrial tubules (Figure 1c).

Nucleoid size and organization are also regulated by members of a recently discovered protein complex that

Figure 1



Overview of how mitochondrial organization contributes to mtDNA organization. **(a)** A hypothetical mitochondrial-ER contact division site highlighting multiple processes implicated in regulating mitochondrial division in both yeast and mammalian cells. The ER, Drp1 (Dnm1 in yeast), the ER formin INF-2, and polymerized F-actin are localized to sites of mitochondrial fission in mammalian cells. In yeast, the ERMES complex also localizes at these division sites to generate the ER-mitochondrial contact. mtDNA nucleoids are located adjacent to both the division sites and the MitOS/MINOS/MICOS complex, which is located at the inner-membrane cristae junctions along the mitochondrial tubules. **(b)** A recently divided mitochondrial tubule. Each newly generated mitochondrial tubule contains its own mtDNA nucleoid, as seen in the majority of division events in yeast cells. **(c)** A mitochondrial tubule in which mitochondrial fission has been blocked. This leads to hyperfused mitochondria (not shown) and enlarged and clustered nucleoids that generate bulging of the tubules. **(d)** A mitochondrial tubule lacking the MitOS complex members Fcj1 and/or Mos1. In the absence of these molecules, nucleoids become enlarged, internal cristae structure is disorganized, and mitochondrial tubular morphology is impacted.

functions in generating proper mitochondrial organization. This complex, known as MitOS/MINOS/MICOS (Mitochondrial Organizing Structure/Mitochondrial Inner-membrane Organizing System/Mitochondrial Contact Site), localizes to the inter-cristae junctions that separate the inner boundary membrane from the cristae and is involved in maintaining proper organization of internal mitochondrial membrane structures and cristae morphology (Figure 1a) (reviewed in [17]). Two of its members, Fcj1 (mitofilin/MINOS2 in mammalian cells) and Mos1/Mio10/Mcs10 (MINOS1 in mammalian cells), were found to regulate nucleoid size and distribution in yeast cells (Figure 1d) [16•]. In their absence cells with very large nucleoids could exhibit dramatic alterations of mitochondrial tubular morphology, at the extremes generating giant hollow spherical mitochondria. The frequency of these grossly misshapen mitochondria increased when mitochondrial fission was additionally impaired, emphasizing the importance of maintaining proper mitochondrial network organization through mitochondrial dynamics. However, only a small portion of cells lose their ability to maintain normal mtDNA nucleoid size and display aberrant mitochondrial morphology when Fcj, Mos1, or Dnm1 (the yeast Drp1) are absent, indicating that other mechanisms exist regulating mtDNA nucleoid organization. On the other hand, ATP20 and ATP21, two other proteins in yeast known to regulate cristae membrane structure, could rescue the enlarged nucleoids generated in the absence of Fcj1 or Mos10. It will be interesting to dissect the specific contributions of each of these different internal membrane-shaping proteins to mtDNA nucleoid organization. The mechanisms by which internal membrane ultrastructure regulates mtDNA organization remain unknown. However, decreased fission alone can lead to similar mtDNA phenotypes, presumably because this leads to the loss of normal mitochondrial tubule separation, thus permitting the mtDNA nucleoids to cluster. Inter-cristae junctions contribute to maintaining proper internal membrane compartmentalization. Therefore, perhaps the loss of these junctions similarly leads to clustering and mis-segregation of mtDNA nucleoids due to loss of proper compartmental localization of the mtDNA within the mitochondrial tubules.

These recent studies demonstrate that mitochondrial dynamics, internal membrane organization, and tubular network morphology are all required to properly organize and distribute the mtDNA throughout the mitochondrial network. Intriguingly, the ER (endoplasmic reticulum), known to contact mitochondria closely at specific sites and participate in mitochondrial division (reviewed in [3,4]), may contribute to mtDNA organization as well. In yeast, the well-characterized ERMES complex (ER-mitochondria encounter structure) regulates mitochondrial-ER contact sites. Recently the ERMES complex was shown to be at the majority (over 60%) of mitochondrial division sites where its members, together with the ER, participate in the initiation and resolution of mitochondrial fission (Figure 1a) [13••]. ERMES members are also known to be associated with mtDNA nucleoids and exhibit functional interactions with the MitOS complex (reviewed in [17]).

These recent discoveries underscore the importance of considering mitochondrial organization and dynamics not in isolation but integrated within the greater context of overall cellular organization. For example, a recent super-resolution microscopy study found that the density of the MitOS complex within the mitochondrial network varied as a function of the mitochondrial proximity to the