

Mitochondrial inheritance is mediated by microtubules in mammalian cell division

Elizabeth Lawrence* and Craig Mandato

Department of Anatomy & Cell Biology; McGill University; Montreal, QC Canada

The mitochondrial network fragments and becomes uniformly dispersed within the cytoplasm when mammalian cells enter mitosis. Such morphology and distribution of mitochondria was previously thought to facilitate the stochastic inheritance of mitochondria by daughter cells. In contrast, we recently reported that mitochondria in dividing mammalian cells are inherited by an ordered mechanism of inheritance mediated by microtubules. We showed that mitochondria are progressively enriched at the cell equator and depleted at the poles throughout division. Furthermore, the mitochondrial distribution during division is dependent on microtubules, indicating an ordered inheritance strategy. The microtubule-mediated positioning of mitochondria in dividing mammalian cells may have functional consequences for cell division and/or mitochondrial inheritance.

Mitochondria are dynamic organelles that perform diverse cellular functions.¹ In addition to providing ATP, mitochondria produce intracellular reactive oxygen species (ROS), buffer cytosolic calcium, produce biosynthetic precursors, play a central role in cell signaling pathways, and initiate cell stress responses, including apoptosis and autophagy. Mitochondria are essential for cell viability and therefore must be accurately inherited during cell division in order to generate viable daughter cells. Therefore, the dividing cell employs partitioning strategies to ensure that each daughter cell inherits equal complements of mitochondria as well as other subcellular organelles.

There are 2 proposed mechanisms governing organelle inheritance.²⁻⁴ The first is a stochastic mechanism based on the laws of probability. Equal partitioning of an organelle by a stochastic process requires that the organelle be present in high copy number and uniformly distributed throughout the mitotic cell cytoplasm. For large, low-copy organelles, this can be achieved by fragmentation when the cell enters mitosis.⁵⁻⁷ Subsequently, when the cell undergoes cytokinesis, equivalent-sized daughter cells are generated, containing approximately equal complements of the organelle. The second type of inheritance strategy is an ordered process in which organelles are actively delivered by the cytoskeleton into daughter cells. An example of ordered inheritance is the robust segregation of chromosomes into daughter cells by microtubules of the mitotic spindle.⁸ In addition, organelles including the Golgi, endosomes, and lysosomes are inherited by ordered mechanisms requiring the mitotic spindle microtubules.⁹⁻¹² A combination of both strategies is used to inherit certain organelles. For example, the Golgi first fragments to generate a high copy number and then utilizes the spindle in order to accurately partition the Golgi fragments between daughter cells.^{6,7}

Mitochondrial inheritance in mammalian cells is proposed to occur via a stochastic process relying on the fragmentation and dispersal of mitochondria upon mitotic entry.²⁻⁴ In support of this, Taguchi et al.⁵ showed that the mitochondrial fission protein, Drp1, is phosphorylated when the cell enters mitosis,

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*Correspondence to: Elizabeth Lawrence;
Email: beth.lawrence@mail.mcgill.ca

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leading to extensive mitochondrial fragmentation. Studies in other systems, however, have indicated the utilization of an ordered mitochondrial inheritance mechanism mediated by the cytoskeleton.¹³⁻¹⁹ For example, experiments in budding yeast demonstrated that mitochondria are transported into the emerging bud via interaction with the actin cytoskeleton,¹³⁻¹⁵ while mitochondria in fission yeast are actively segregated by the microtubules of the spindle poles.¹⁶ The microtubules of the spindle have also been implicated in mitochondrial inheritance in higher eukaryotes.¹⁷⁻¹⁹ Furthermore, 2 previous studies in porcine oocytes and mouse pancreatic cells reported an enrichment of mitochondria at the cleavage furrow,^{20,21} suggesting that mitochondrial positioning and inheritance is also regulated in these systems.

We recently demonstrated that mitochondria are inherited by an ordered microtubule-mediated mechanism in mammalian cell division.²² Characterization of the mitochondrial distribution during HeLa cell division showed that, initially, in metaphase, the mitochondria were evenly dispersed within the cytoplasm, supportive of a stochastic partitioning strategy. However, as division proceeded, the mitochondria became progressively enriched at the

cell equator in the region of the cytokinetic cleavage furrow and depleted at the cell poles. Therefore, the homogenous distribution of mitochondria required for accurate stochastic inheritance was not maintained throughout division. Furthermore, disruption of the microtubules inhibited the enrichment of mitochondria at the cleavage furrow, indicating that the distribution of mitochondria in dividing mammalian cells is dependent on microtubules. Thus, we showed for the first time that mitochondrial inheritance during mammalian cell division occurs via an ordered process that is dependent on microtubules.

A stochastic inheritance mechanism would be sufficiently accurate if the mitochondria simply remained fragmented and uniformly distributed in the cytoplasm throughout the entire division process.² It is interesting, therefore, to consider why the mitochondria are fragmented and homogeneously dispersed in metaphase but are subsequently polarized by the microtubules toward the cleavage furrow in cytokinesis.²² One explanation is that the mitochondria are specifically recruited to the cleavage furrow to perform a function. For example, mitochondrial activity, such as ATP production, calcium buffering, or ROS production may be required in proximity to the

cleavage furrow, spindle, or midbody in order to facilitate cytokinesis. Another possibility is that the microtubules actively regulate mitochondrial inheritance. For example, pooling the mitochondria at the equator of the dividing parent cell might promote mixing of the mitochondrial population to ensure that each daughter cell receives a heterogeneous complement of mitochondria.

In summary, mitochondria are partitioned into daughter cells by an ordered, microtubule-mediated mechanism of inheritance in mammalian cell division. As division proceeds, mitochondria are progressively enriched at the cytokinetic cleavage furrow and depleted at the cell poles in a microtubule-dependent manner. Whether the specific enrichment of mitochondria at the cleavage furrow is functionally significant for mitochondrial inheritance or cell division is unknown and will be the focus of future studies.

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No potential conflicts of interest were disclosed.

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