Detaching the tether: Remodeling mitochondrial localization during meiosis

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During meiosis, many organelles including mitochondria undergo dramatic remodeling to be inherited in gametes. In this issue, new work from Sawyer et al. (2019. J. Cell. Biol. https://doi.org/10.1083/jcb.201807097) demonstrates that the developmentally programmed destruction of a tether releases mitochondria from the cell cortex during meiosis in budding yeast.

Inheritance of organelles during cell division requires their active positioning within the cell so that they become incorporated into each daughter cell. This precise positioning is especially important for mitochondrion, an organelle that contains its own genome and therefore cannot be made de novo. The regulation of tethering is critical to this process, as tethers link mitochondria to cellular structures and maintain their localization at specific subcellular positions (1). In cells that undergo asymmetric divisions, tethers safeguard the inheritance of mitochondria. For example, in budding yeast, mother- and bud-specific tethers anchor mitochondria to the cell cortex in mother cells and to the bud tip in daughter cells, ensuring that both mother and daughter cells retain mitochondria after cytokinesis. How cells regulate the subcellular localization of mitochondria during the cell cycle and during differentiation is an exciting area of investigation.

The process of gametogenesis in budding yeast provides an example of a cell division and differentiation pathway that requires extensive remodeling of the subcellular localization of mitochondria. During gametogenesis, cells undergo the two meiotic chromosomal divisions, creating four haploid nuclei that are then packaged into spores (2). Unlike the asymmetric division of mitosis, in which the nucleus divides across the bud neck, meiosis occurs in the mother cell and four daughter cells are formed within the mother cell cytoplasm. After the daughter cells differentiate into spores by first enveloping each nucleus in a new prospore membrane and then assembling a spore wall, the anucleate mother cell matures into an ascus that encapsulates the four spores. For inheritance of the mitochondria into spores, it is imperative that mitochondria are redistributed from their initial localization at the mother cell plasma membrane to surround each nucleus. Initial observations demonstrated that mitochondria lose their cell cortex localization as cells undergo the meiotic divisions and that 55% of the mitochondria are incorporated into spores (3–5). How mitochondrial remodeling is regulated in meiosis has remained a long unanswered question.

In this issue, Sawyer et al. provide new insight into this process by addressing the question of how mitochondria are released from the plasma membrane during meiosis (6). Using time-lapse fluorescence microscopy, the authors found that detachment of mitochondria from the plasma membrane was coincident with anaphase II spindle elongation. Because the timing was precise, they asked if a known cell cycle regulator governs mitochondrial release. Many known regulators of chromosome segregation, such as polo kinase, cyclin-dependent kinase, and mitotic cyclins, did not have a role in regulating mitochondrial release. Main regulators of chromosome segregation, such as polo kinase, cyclin-dependent kinase, and the anaphase-promoting complex coactivator Cdc20, did not have a role in regulating mitochondrial detachment. Interestingly, loss of these proteins caused cells to arrest in meiosis I with undivided nuclei; however, mitochondrial detachment still occurred with similar timing as in wild-type cells. These results suggested that mitochondrial detachment occurred independently of, but coincident with, meiosis II chromosome segregation.

The middle meiosis transcription factor Ndt80 was required for mitochondrial detachment. In the absence of Ndt80, cells arrested in prophase I (7) and did not detach mitochondria (6). This led Sawyer et al. to ask if Ndt80 induced transcription of a gene required for mitochondrial detachment (6). One candidate was the meiosis-specific kinase called Ime2. Although IME2 is also expressed in early meiosis, Ndt80 transcription of IME2 dramatically increases Ime2 levels (8). Using an allele of Ime2 that can be selectively inhibited, the authors found that mitochondria retained cell cortex localization with inhibition of Ime2 (6). Furthermore, with hyperactive Ime2 expression, mitochondria detached from the cell cortex in cells arrested in prophase I due to a deletion of NDT80. These experiments identified Ime2 as a major regulator of mitochondrial remodeling in meiosis.

How does Ime2 regulate mitochondrial detachment? To address this question, the authors investigated the mitochondria–ER–cortex anchor (MECA) that tethers mitochondria to the plasma membrane and has two known components: Num1 and Mdm36 (9, 10). Several experiments demonstrated that Ime2 regulates tether release (6). First, Ime2 phosphorylated Num1 and Mdm36 in vitro. Second, in vivo, Num1 was phosphorylated on a specific residue only when Ime2 activity was high. Third, Num1 and Mdm36 foci were retained at the cell cortex with inhibition of Ime2. Fourth, Num1 and Mdm36 protein levels decreased in meiosis II, and inhibition of Ime2 attenuated this decline. Finally, hyperactive Ime2 in prophase I resulted in fewer Num1 foci, suggesting that Ime2 activity resulted in the loss of localized Num1. Overall, their experiments demonstrate that Ime2 phosphorylates Num1 and Mdm36, which leads to their degradation.
The work highlighted here provides a beautiful example of how mitochondrial tethering is regulated during development to govern the distribution and inheritance of the mitochondrial network. As cells enter meiosis II, the Ime2 kinase becomes highly active and phosphorylates and inactivates the MECA tether, releasing the mitochondria from the plasma membrane (Fig. 1). In the future, it will be interesting to further investigate how the mitochondria accumulate around the nuclei for incorporation into the spores. Are the mitochondria actively trafficked to the nuclear envelope? Are mitochondria tethered to the nuclear envelope to ensure their encapsulation into spores? Are there regulatory mechanisms to ensure a certain number of mitochondria incorporate into each spore and that all four spores inherit mitochondria? Answers to these questions will provide further insight into the regulation of mitochondrial inheritance in gametes. Although several of the details of this mechanism may be specific to budding yeast, the regulation of tethering is likely a conserved mechanism for remodeling of mitochondrial subcellular localization during development.

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