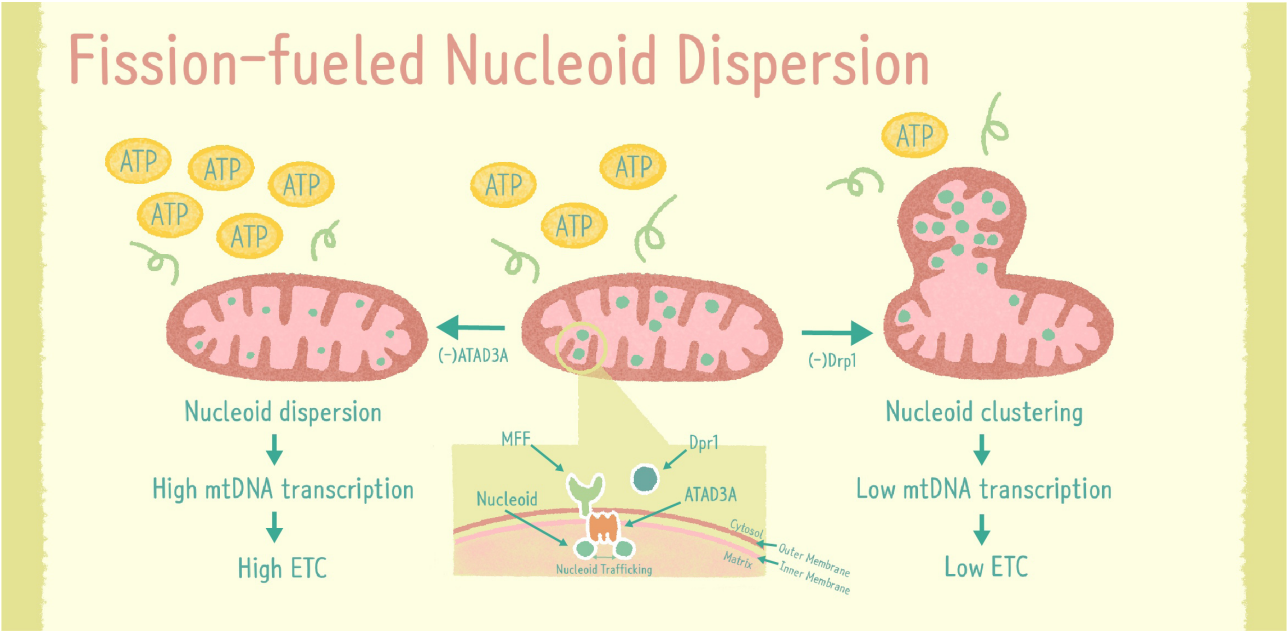
Molecules and Cells

Journal Club

Fission-Fueled Nucleoid Dispersion, a Novel Mitochondrial Metabolic Activation Mechanism

Jeongah Kim*

Department of Anatomy, College of Medicine, Korea University, Seoul 02841, Korea
*Correspondence: jakim0413@korea.ac.kr
https://doi.org/10.14348/molcells.2023.0043
www.molcells.org



Local regulation of the mitochondrial DNA (mtDNA) transcription within the mitochondria contributes to regulate the respiratory activity by sensing the nucleoid distribution. This is a new regulatory respiratory function within the mitochondria. Moreover, the coordination of mitochondrial fission and nucleoid trafficking, mediated by dynamin-related protein 1 (Drp1) and ATPase family AAA domain-containing protein 3A (ATAD3A), regulates the nucleoid distribution. However, defects in the Drp1-mediated fission results in low electron transport chain (ETC) formation due to the low transcription of the mtDNA, while the ATAD3A-mediated nucleoid dispersion led to high ETC formation due to the high transcription of the mtDNA. Additionally, the Drp1-MFF-ATAD3A-nucleoid cascade mediates the communication between the cytosolic mitochondrial fission and mitochondrial matrix nucleoid function. MFF, mitochondrial fission factor.

Received March 14, 2023; accepted March 23, 2023; published online April 27, 2023

eISSN: 0219-1032

Mitochondria are endosymbiotic organelles that evolved from α-proteobacteria and still share many similarities with free-living organisms. For instance, they continuously move within the cells and change shape through spontaneous fission and fusion cycles. Furthermore, they have their own unique genome which encodes the proteins that form the respiratory subunits and other RNAs for mitochondria-specific translation. Analogous to the nuclear genome, mitochondrial DNA (mtDNA) is also packaged into nucleoids, which appear as dot-like structures when observed under a fluorescence microscope (Nicholls and Gustafsson, 2018). The amount and activity of mtDNA are closely associated with cellular bioenergetics through the mitochondrial oxidative phosphorylation. For example, mitochondrial biogenesis increases the mtDNA copy number in response to physiological stimuli, and this regulation is mediated by the master regulator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) (Gureev et al., 2019). PGC1α induces the synchronous expression of nuclear and mitochondrial genes. It is believed that the maintenance and expression of mtDNA are regulated by receiving nuclear signals, rather than local regulation in mitochondria.

An interesting observation regarding the nucleoid behavior is its association with mitochondrial fission. It is known that mitochondrial fission and the location of the nucleoids are spatially linked at the endoplasmic reticulum (ER)–mitochondria contact site (Lewis et al., 2016). The nucleoids that are engaged in replication, spatially mark the mitochondrial division at the ER–mitochondrial contact site. The mitochondrial fission occurs as a successive event after the mtDNA replication through the recruitment of the dynamin-related protein 1 (Drp1), which is a central molecule for mitochondrial fission. Defects in the Drp1 activity induces nucleoid clustering in the mitochondrial matrix, called as a mitobulb (Ban-Ishihara et al., 2013). However, considering that Drp1 is exclusively localized in the cytosol, it is unknown how Drp1 recognizes and influences the nucleoids within the mitochondrial matrix across the double membrane.

Ishihara et al. (2022) provided a new insight into this perspective. They discovered that the ATPase family AAA domain-containing protein 3A (ATAD3A) is the molecule that links the spatial regulation of the cytosolic fission and matrix nucleoid function. They revealed that the mitochondrial fission factor (MFF), which acts as a receptor for Drp1 in the outer membrane, and nucleoids in the matrix can interact with the inner membrane-anchored protein, ATAD3A. It is well-known that the ATAD3A protein influences the cristae morphology, mtDNA replication, and cholesterol levels (Arguello et al., 2021; Peralta et al., 2018). They discovered that ATAD3A is required for the formation of the mitobulb in Drp1-deficient cells, which suggests that ATAD3A-mediated nucleoid trafficking is necessary for nucleoid distribution (Ishihara et al., 2022). What is the physiological role of the morphology and dynamics of the nucleoid? The dispersed nucleoids in ATAD3A-deficient cells were more efficient at transcribing genes encoding the respiratory subunits. Furthermore, the decreased biogenesis of the respiratory subunit chain due to fission arrest was rescued through ATAD3A inactivation. These results indicate that the proper nucleoid distribution is important for respiratory function. Coordination of mitochondrial fission and the nucleoid dispersion is mediated by the Drp1-MFF-ATAD3A-nucleoid cascade that relays communication between the cytosol and mitochondrial matrix. It has become evident that there is a local regulatory process that occurs within mitochondria, sensing the internal nucleoid distribution, rather than simply receiving the signals by the nucleus for mtDNA transcription.

The new findings in this study have raised many intriguing questions for further investigation. Are there any permissive mechanisms that allow ATAD3-mediated nucleoid trafficking? More specifically, are structural changes in the mitochondrial cristae required for nucleoid dispersion? This is especially significant because previous research has shown that both Drp1 and ATAD3A help to remodel the inner membrane and/or cristae of mitochondria (Cho et al., 2017; Peralta et al., 2018). The Drp1- and ATAD3A-dependent remodeling of the inner mitochondrial compartment may be a permissive requirement for the enhanced nucleoid dispersion within the mitochondrial matrix. In addition, given that the mtDNA replication and transcription are inversely connected (Agaronyan et al., 2015), does the nucleoid trafficking have an impact on mtDNA replication? Could the appropriate nucleoid trafficking have a role in nucleoid/mitochondrial quality control? An in-depth analysis of these and related questions will facilitate an increased understanding of why and how the mitochondrial matrix and exterior cytosolic environment of the mitochondria are closely linked.

ACKNOWLEDGMENTS

This work was supported by grants from the National Research Foundation of Korea (NRF-2021R1A2C1010677).

CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

ORCID

Jeongah Kim https://orcid.org/0009-0003-5355-9713

REFERENCES

Agaronyan, K., Morozov, Y.I., Anikin, M., and Temiakov, D. (2015). Replication-transcription switch inhuman mitochondria. Science *347*, 548-551.

Arguello, T., Peralta, S., Antonicka, H., Gaidosh, G., Diaz, F., Tu, Y.T., Garcia, S., Shiekhattar, R., Barrientos, A., and Moraes, C.T. (2021). ATAD3A has a scaffolding role regulating mitochondria inner membrane structure and protein assembly. Cell Rep. *37*, 110139.

Ban-Ishihara, R., Ishihara, T., Sasaki, N., Mihara, K., and Ishihara, N. (2013). Dynamics of nucleoid structure regulated by mitochondrial fission contributes to cristae reformation and release of cytochrome c. Proc. Natl. Acad. Sci. U. S. A. *110*, 11863-11868.

Cho, B., Cho, H.M., Jo, Y., Kim, H.D., Song, M., Moon, C., Kim, H., Kim, K., Sesaki, H., Rhyu, I.J., et al. (2017). Constriction of the mitochondrial inner compartment is a priming event for mitochondrial division. Nat. Commun. *8*, 15754.

Gureev, A.P., Shaforostova, E.A., and Popov, V.N. (2019). Regulation of mitochondrial biogenesis as a way for active longevity: interaction between the Nrf2 and PGC-1alpha signaling pathways. Front. Genet. *10*, 435.

Ishihara, T., Ban-Ishihara, R., Ota, A., and Ishihara, N. (2022). Mitochondrial nucleoid trafficking regulated by the inner-membrane AAA-ATPase ATAD3A modulates respiratory complex formation. Proc. Natl. Acad. Sci. U. S. A. *119*, e2210730119.

Lewis, S.C., Uchiyama, L.F., and Nunnari, J. (2016). ER-mitochondria contacts couple mtDNA synthesis with mitochondrial division in human cells. Science *353*, aaf5549.

Nicholls, T.J. and Gustafsson, C.M. (2018). Separating and segregating the human mitochondrial genome. Trends Biochem. Sci. *43*, 869-881.

Peralta, S., Goffart, S., Williams, S.L., Diaz, F., Garcia, S., Nissanka, N., Area-Gomez, E., Pohjoismaki, J., and Moraes, C.T. (2018). ATAD3 controls mitochondrial cristae structure in mouse muscle, influencing mtDNA replication and cholesterol levels. J. Cell Sci. *131*, jcs217075.