Improving mitochondrial function by controlling mitochondrial DNA movement

Department of Biological Sciences, Graduate School of Science
Professor Naotada Ishihara
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Abstract

We have shown that a molecule known as ATAD3A is essential for the movement of genetic material inside intracellular substructures called mitochondria. Appropriate distribution of mitochondrial DNA (mtDNA), organized into "nucleoid" structures, is key for the generation of energy by the "respiratory chain" protein complex. This study opens up opportunities for developing new methods to alter nucleoid movement and affect mitochondrial function, thereby providing potential therapies against mitochondrial diseases.

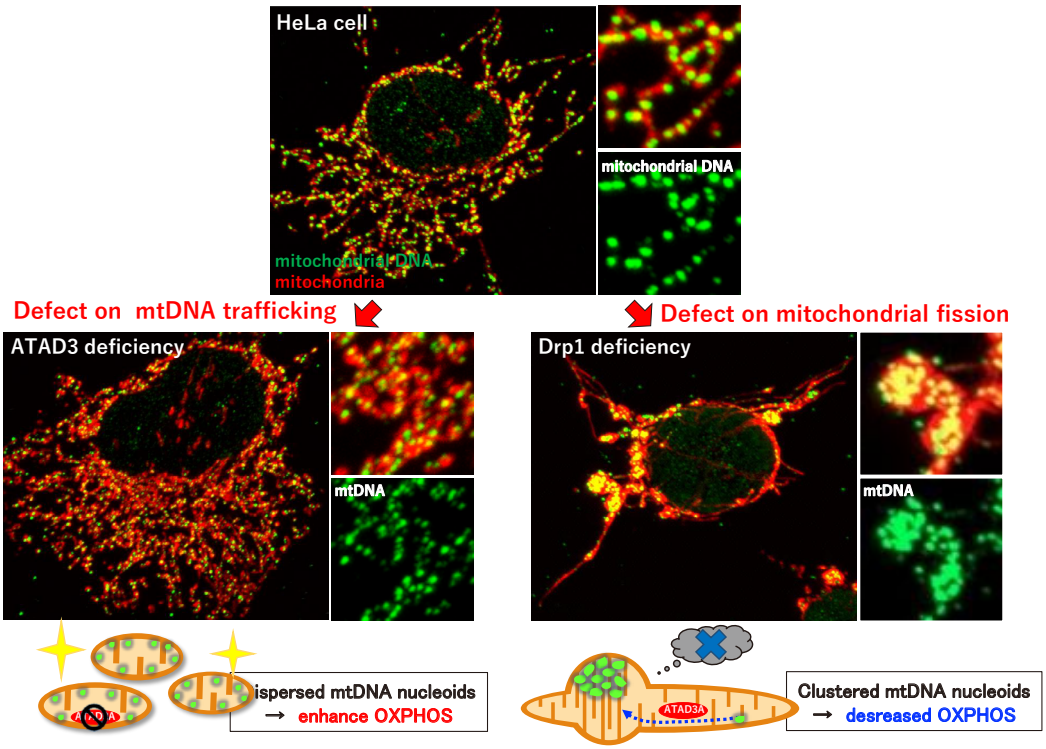
Background & Results

Mitochondria, famously known as the powerhouse of the cell, are important cellular structures that are vital for their role of generating energy. Mitochondria are "dynamic", meaning they constantly fuse together and split apart. They contain a small amount of genetic information known as mitochondrial DNA (mtDNA). The mtDNA, organized into dot-like structures called "nucleoids", also moves around inside the mitochondria. We had previously shown that the movement of the nucleoids is linked to the fission of mitochondria. However, the mechanisms and function of this movement were unclear.

Here we have identified a molecule known as ATAD3A that is essential for nucleoid movement and could be a potential therapeutic candidate for mitochondrial diseases. ATAD3A, which is anchored to the inner mitochondrial membrane, mediated the interaction of mtDNA nucleoids (present inside the mitochondria) with factors involved in mitochondrial fission (present on the outer mitochondrial membrane). They demonstrated that ATAD3A was essential for the active movement of mtDNA nucleoids within the mitochondria—a process called nucleoid "trafficking"—and that nucleoids were abnormally clustered in cells that lack mitochondrial fission. Together, mitochondrial fission and nucleoid trafficking determine the size, number, and distribution of the nucleoids within the mitochondria, and that regulation of nucleoid dynamics is crucial for the maintenance of respiratory chain complexes on the mitochondrial inner membrane.

Significance of the research and Future perspective

The distribution of nucleoids throughout the mitochondrial network activates expression of the mtDNA and increases formation of the "respiratory chain complex", which is a group of several protein complexes essential for energy production within cells, and the correct distribution of the mtDNA nucleoids is key for efficient energy production. The development of techniques to alter mtDNA movement may help regulate mitochondrial function in the future. Therefore, not only does this work increase our knowledge of the regulatory processes in mitochondria but it also provides scope for developing future therapies against abnormal mitochondrial functioning.



Patent
Treatise Ishihara, Takaya et al. Mitochondrial nucleoid trafficking regulated by the inner-membrane AAA-ATPase ATAD3A modulates respiratory complex formation. Proceedings of the National Academy of Science of the United States of America. 2022, 119 (47): e2210730119. doi: 10.1073/pnas.2210730119
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