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Newly identified role for 'power plants' in human cells could lead to targeted therapies

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Scientists have determined that human cells are able to shift important gene products into their own mitochondria, considered the power plants of cells. The finding could eventually lead to therapies for dozens of diseases.

The gene products, known as tRNAs, assemble amino acids for the production of proteins within mitochondria. If the mitochondrial tRNA genes are defective or missing, and proteins are not manufactured, the mitochondria are unable to generate adequate energy.

Defective tRNAs are believed to be the cause of about 60 percent of conditions traced to malfunctions in the mitochondria. The range of related conditions includes diabetes, hearing loss and a number of neurological disorders, depending on which kinds of cells are affected.

Mitochondria are encased in their own membrane, making them a structure that is complicated to study. Previous research has suggested that only in lower organisms, such as protozoans, yeast and plants, can tRNAs be imported to the mitochondria from the cell cytoplasm, the fluid-based area that contains most components of a cell.

But in this new research, scientists determined that tRNAs can be imported from cytoplasm to mitochondria in rat liver cells and human cells as well.

"This was totally unexpected, to find an innate, built-in mechanism that

we humans have," said Juan Alfonzo, senior author of the study and an assistant professor of microbiology at Ohio State University. The finding broadens the study of therapeutic options involving attempts to introduce healthy tRNAs to the defective mitochondria of ill patients, Alfonzo said.

"If you have a mutation in a tRNA that you suspect is involved in disease, you theoretically should be able to bring a healthy tRNA from the cytoplasm into the mitochondria and correct the malfunction," he said.

The research appears online this week in the *Proceedings of the National Academy of Sciences*.

Alfonzo noted that the current study was able to determine that the import of tRNAs occurs, but it leaves open the question of how it happens.

He and colleagues conducted experiments first in rat liver cells to test whether tRNA import occurs in mammals at all. When the import was observed in rat mitochondria, they extended the study to human cells.

The finding that tRNA import occurs in humans can set in motion an entirely new line of research into therapeutic options for patients with diseases caused by mitochondrial defects. There appears to be no way to introduce healthy tRNAs directly into mitochondria because their membranes have proven impenetrable to such outside interference, Alfonzo explained.

So scientists know they would have to rely on the import process that starts in the cytoplasm to transfer healthy tRNAs to damaged mitochondria and improve energy production.

Until now, researchers didn't know the human mitochondria had that import ability, so scientists were going to try using protozoan or yeast cells to manipulate the import process in human cells.

"What we are saying is you don't need to bring up new machinery from a different organism because human cells already come equipped with their own way to import tRNAs. There is no need to cross species," Alfonzo said. "What we need to know now is what proteins are involved in the import mechanism so we can exploit the process for therapy."

One compound already identified as essential for the process is Adenosine-5-triphosphate, or ATP, a compound associated with energy transport in cells. Alfonzo and colleagues demonstrated ATP's role in the process using cells from a patient with a specific type of epilepsy called MERRF. This disease is characterized by a mitochondrial tRNA mutation leading to a drastic reduction in the mitochondria's ability to generate ATP, which in turn hinders the import of tRNAs into the mitochondria of people with this disease.

When ATP was introduced to the mitochondria of these diseased cells, the import process of tRNAs from the cytoplasm to the mitochondria was restored.

"These were cells from an actual patient, so this also makes the argument that we don't need a surrogate system from other organisms to set the import process in motion," Alfonzo said.

Source: Ohio State University

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