Scientists find hints for how a fatty compound functions in the cell's powerhouse

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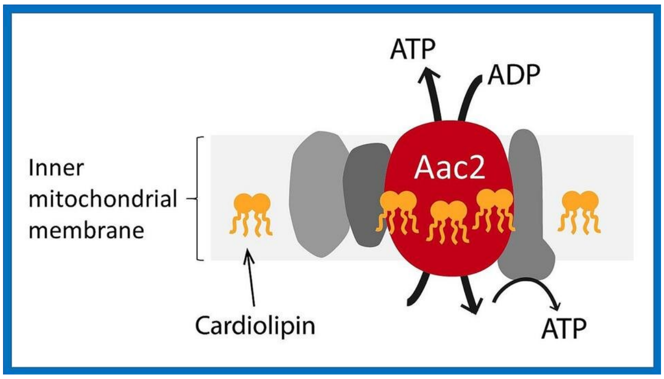

How a fatty compound called cardiolipin helps the transport protein Aac2 get the building blocks of the cellular energy molecule ATP into mitochondria for assembly and then, send completed ATPs out into the body. Credit: Nanami Senoo, Steven Claypool Laboratory, Johns Hopkins Medicine

In a study of yeast, Johns Hopkins Medicine researchers say they have found how a fatty compound called cardiolipin helps create cellular energy. The researchers say their findings will help shed light on conditions that impact human metabolism, such as heart disease, diabetes and Barth syndrome, a rare genetic disorder that weakens the heart.

Cardiolipin is found in almost every one of the body's cells and resides within the labyrinth of membranes that make up mitochondria. It's thought to help mitochondria create adenosine triphosphate (ATP), the molecule that fuels cell metabolism. Cardiolipin has been implicated in a number of metabolic and immune diseases, including blood clotting disorders caused by an abnormal immune reaction to the fatty molecule.

In its study published Aug. 28, 2020, in *Science Advances*, the Johns Hopkins Medicine team found how cardiolipin helps stabilize other structures within mitochondrial membranes.

"Mitochondrial membranes are some of the busiest structures in the body, packed with fats and proteins that give our cells the energy they need to keep us alive," says Steven Claypool, Ph.D., professor of physiology at the Johns Hopkins University School of Medicine.

Within this membrane matrix is an important transport protein called Aac2 that ships the building blocks of ATP into the mitochondria and then moves activated ATP out into the cell. Previous studies hinted that cardiolipin was important in helping Aac2 transport proteins do their job. However, not much was known about this process.

Claypool and his colleagues found that three areas on Aac2 where cardiolipin binds help Aac2 stay in the right shape to transport ATP. They found that yeast cells engineered to lack cardiolipin did not produce cellular energy as efficiently as yeast cells with abundant cardiolipin levels.

In further experiments analyzing how proteins interacted in the membrane, the researchers found that links between Aac2 and the rest of the ATP production line—known as respiratory supercomplexes—also are dependent on the presence of cardiolipin.

The researchers speculate that cardiolipin-protein interactions in mitochondrial membranes evolved as a way to streamline energy production. They believe this occurs by connecting Aac2 with the respiratory supercomplexes that supply ATP materials or by using cardiolipin to protect the membrane proteins from being jostled out of place.

Overall, these results suggest that changes in cardiolipin structure or production could be linked with diseases, say the researchers.

"We may need to look closer at cardiolipin structure or production in diseases or conditions in which cardiolipin metabolism has been implicated," says Claypool.

Claypool and his colleagues are developing new tools to analyze the fats in mitochondrial membranes to study protein-cardiolipin interactions.

More information: N. Senoo et al. Cardiolipin, conformation, and respiratory complex-dependent oligomerization of the major mitochondrial ADP/ATP carrier in yeast, *Science Advances* (2020). DOI: 10.1126/sciadv.abb0780