MiNT protein a fresh target to attack disease

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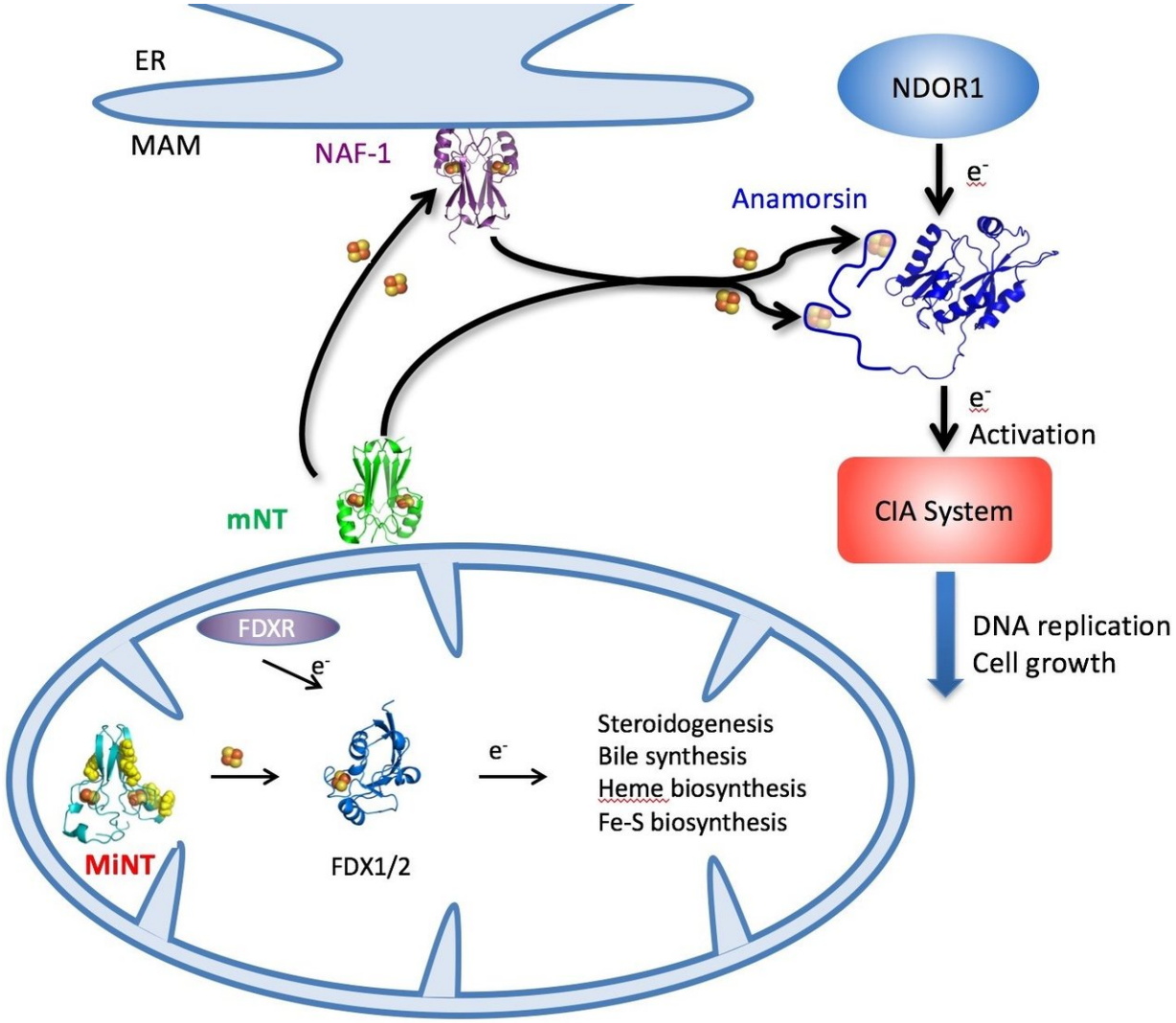

An illustration outlines the NEET cycle in cells by which iron-sulfur clusters are delivered by MiNT, mitoNEET (mNT) and NAF-1 proteins in the cytosol or the mitochondria (bottom) to an array of cellular metabolic processes, including the synthesis of ATP. Credit: Patricia Jennings/University of California at San Diego

A two-faced protein in a chain that regulates iron and other elements in cells could provide a new target to treat cancer, diabetes and other diseases.

A team of researchers at Rice University, the University of California at San Diego (UCSD), the Hebrew University of Jerusalem and the University of North Texas detailed the structure of a protein called mitochondrial inner NEET (MiNT), part of a pathway that stabilizes mitochondria, the organelles that produce energy for cells.

Their report appears this week in the *Proceedings of the National Academy of Sciences*.

MiNT is distinct from its cousins, the NEET proteins mitoNEET and NAF-1, but they all play a part in the progression of cancer, diabetes, neurodegenerative diseases and aging. NEET proteins have been a focus for the team that previously reported their significance in binding toxic clusters of iron and sulfur in cells and as a possible target to treat breast cancer.

In the new study, the researchers led by longtime collaborators Patricia Jennings at UCSD and José Onuchic at Rice's Center for Theoretical Biological Physics (CTBP) became the first to detail the crystalline structure of MiNT, also known as CISD3, which resides inside mitochondria.

Jennings and her team produced the molecular structure. With it, they were able to show that while MiNT shares some characteristics with other iron-sulfur proteins in the NEET family, there are significant differences that likely make it the most potent of the three.

MitoNEET and NAF-1 (aka CISD1 and CISD2, respectively) are dimers, proteins with two similar, connected monomers that reside in the cytosol, the fluid inside cells. But MiNT is a monomer that lives exclusively inside mitochondria, where it collects iron-sulfur clusters delivered by the other NEETs and distributes them to facilitate, among other things, the synthesis of adenosine triphosphate (ATP), the molecule that carries energy throughout cells to enable metabolic processes.

MiNT also differs by showing two sides to its environment, one hydrophobic (water-repelling) and the other hydrophilic (water-attracting). "Because it's a monomer, each side is different, so it's going to interact with different proteins, and you may be able to target it with different drugs on each side," said Jennings, a CTBP affiliate and a professor of chemistry and biochemistry at UCSD.

"It's faster and more efficient than the other NEETs," said Onuchic, whose lab built computer simulations to study MiNT's folding dynamics. "It would be very dangerous to have a protein like that in the cytosol;

that's why it's restricted inside the mitochondria, where a lot of bioenergetics processes take place."

The researchers said MiNT is essential to the balance of iron and reactive oxygen species (ROS) in mitochondria. "Iron is toxic," Jennings said. "Too much of it in the cell is bad. We must therefore control it in our bodies because it's so important to energy regulation and key to health and disease.

"With the structure of MiNT, we can begin to understand the complete regulatory loop that controls iron-sulfur clusters and ROS that was not recognized before," she said. "We can begin to see how these proteins regulate flow in and out of the mitochondria."

MiNT's role in ATP production may make it an effective target for shrinking tumors, Onuchic said. Previous experiments with the other NEETs showed downregulating their expression or targeting their centers cut the amount of energy available to cancer cells, which reduces tumor growth.

"Cancer cells need so much more iron than healthy cells with normal iron homeostasis," he said. "When a cell divides, it has to double the ribosomes, and that's energetically very expensive. Because cancer cells divide so quickly, they need much more iron and depend on the NEET cycle to provide it.

"Cancer uses the three NEET proteins because they require so much iron and reactive oxygen," Onuchic said. "What we have noticed—though it's not clear exactly how they work—is that if you knock down any of them, it makes tumors grow smaller. Even if you knock down just one, it reduces cancer growth." Because MiNT is a more prodigious producer of iron and ROS, it may be the most effective of the three to target, he said.

"The discovery of the MiNT structure, dynamics and involvement in mitochondrial iron and ROS accumulation enabled the characterization of the complete NEET human protein family," said co-author Rachel Nechushtai, a professor at the Hebrew University of Jerusalem. "Moreover, it provides our international team the unique opportunity to unravel the interrelationships of the three NEET proteins and to discover in which cellular pathways they are involved.

"The finding that all three iron-sulfur proteins cooperate in the same pathway to protect cancer cells provides an excellent set of targets for cancer therapy," she said.

"The link that NEET proteins provide between iron levels in cancer cells

and the level of reactive oxygen species demonstrates how cancer cells control the balance between a high rate of proliferation and mutations, which is key to our understanding of how to fight cancer," said co-author Ron Mittler, a professor of biological sciences at the University of North Texas.

More information: Colin H. Lipper el al., "Structure of the human monomeric NEET protein MiNT and its role in regulating iron and ROS in cancer cells," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1715842115

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