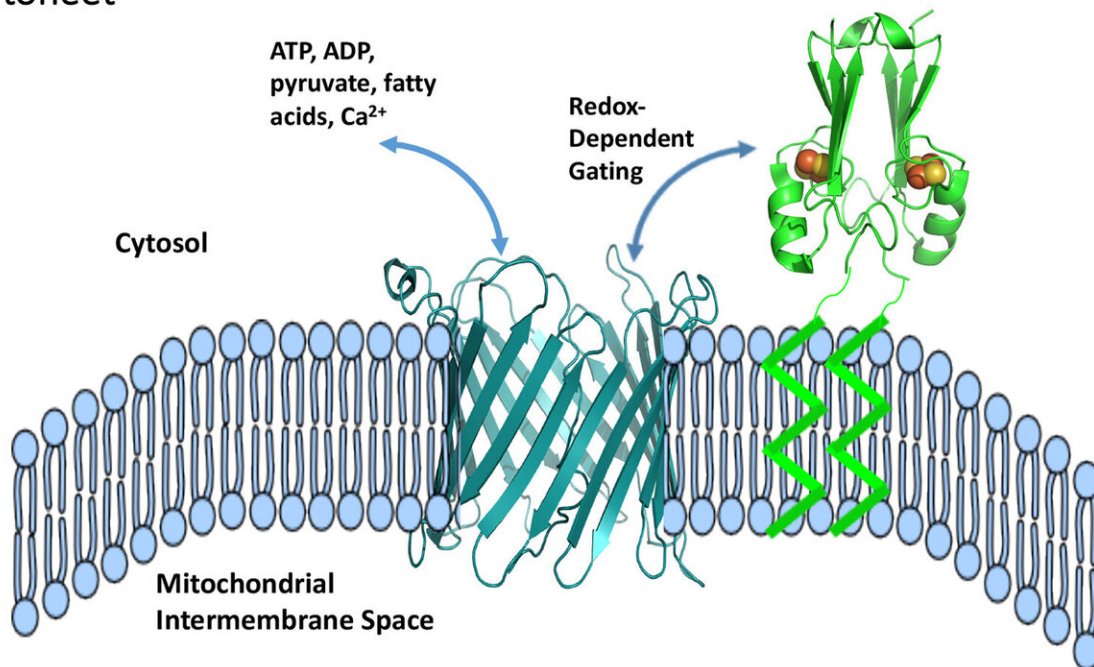


Study points to new drug target in fight against cancer

September 18 2019, by Jade Boyd

Gating of Voltage-Dependent Anion Channel (VDAC) by Oxidized Mitoneet



When oxidized, the protein mitoNEET (green) can close voltage-dependent anion channels, or VDACs (center), passageways that allow metabolites and signaling molecules to pass through the outer membrane (blue band) of the mitochondria, the "power plant" that supplies cells with chemical energy. Credit: CTBP/Rice University

Researchers have identified a potential new drug target in the fight against cancer.

In a study this week in the *Proceedings of the National Academy of Sciences*, an international team of researchers describe how a cancer-linked version of the protein mitoNEET can close the primary gateways in the outer surface of mitochondria, the "power plants" that supply [cells](#) with chemical energy. These gateways, or "voltage-dependent anion channels" (VDACs), normally open and close to allow the passage of metabolites and other small molecules between mitochondria and the rest of the cell.

"The VDAC channel transports all types of metabolites between the cytosol and the mitochondria," said study co-author José Onuchic, a physicist and co-director of Rice University's Center for Theoretical Biological Physics (CTBP). "Dysfunction of this channel is involved in many diseases including cancer and [fatty liver disease](#)."

The research was performed by an international team of computational and structural biologists from CTBP, the University of California, San Diego (UCSD), the Hebrew University of Jerusalem and the University of Missouri-Columbia.

In the study, they detailed how mitoNEET regulates VDAC, and showed that the high-affinity interaction between the two proteins could be disrupted by a drug that targets VDAC.

"In its naturally occurring reduced state in healthy cells, mitoNEET has no measurable affinity for VDAC," said Onuchic, a Cancer Prevention and Research Institute of Texas (CPRIT) Scholar in Cancer Research who led Rice's efforts on the project. "This indicates that the mechanism of interaction is redox-dependent and that targeting of the highly important VDAC complex in diseased states can be fine-tuned."

MitoNEET, a known player in cancer as well as diabetes, aging and Parkinson's disease, is a member of the NEET family of proteins, which transport clusters of iron and sulfur molecules inside cells. These clusters help regulate cells by controlling reduction-oxidation, or redox processes, and metabolism.

MitoNEET naturally adheres to the outer surface of the mitochondria, and the researchers said the direct connection of mitoNEET to VDAC, one of the most abundant proteins in the mitochondrial outer membrane, is significant.

Co-author Patricia Jennings, a structural biologist at UCSD, said, "The discovery that mitoNEET directly gates VDAC, the major porin of mitochondria, as well as the accompanying structural analysis and predictions for this interaction, affords a new platform for investigations of methods to induce cancer cells to commit cell suicide, or apoptosis/ferroptosis, in a cancer-specific, regulated process."

A defining characteristic of cancer progression is altered cellular metabolism. Study co-author Rachel Nechushtai of the Hebrew University said the work suggests it may be possible to regulate the metabolic and functional interactions of VDAC with a drug or drugs that could be useful against several kinds of [cancer](#).

Onuchic said, "Fine-tuning a drug that specifically alters the redox-state of interaction between VDAC and mitoNEET would allow the development of new weapons to battle multiple cancers."

Nechushtai and Jennings first detailed the molecular structure of mitoNEET in 2007, and many of the collaborators on the project have worked together for more than a decade to decipher the workings of mitoNEET and related proteins like NAF-1 and MiNT.

"The junction of iron and redox is key to the control of many different cellular processes involved in many human pathologies," University of Missouri co-author Ron Mittler said. "Identifying a master point of regulation for these processes that is mediated by the mitoNEET-VDAC interaction is a major step forward in our understanding of these processes."

The researchers said longstanding ties between the collaborators and joint funding from both the US and Israel played a key role in the success of the project.

More information: Colin H. Lipper et al, Redox-dependent gating of VDAC by mitoNEET, *Proceedings of the National Academy of Sciences* (2019). [DOI: 10.1073/pnas.1908271116](https://doi.org/10.1073/pnas.1908271116)

Provided by Rice University

Citation: Study points to new drug target in fight against cancer (2019, September 18) retrieved 20 April 2024 from <https://medicalxpress.com/news/2019-09-drug-cancer.html>

| |
|--|
| <p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p> |
|--|