Small proteins play big role in cellular energy balance

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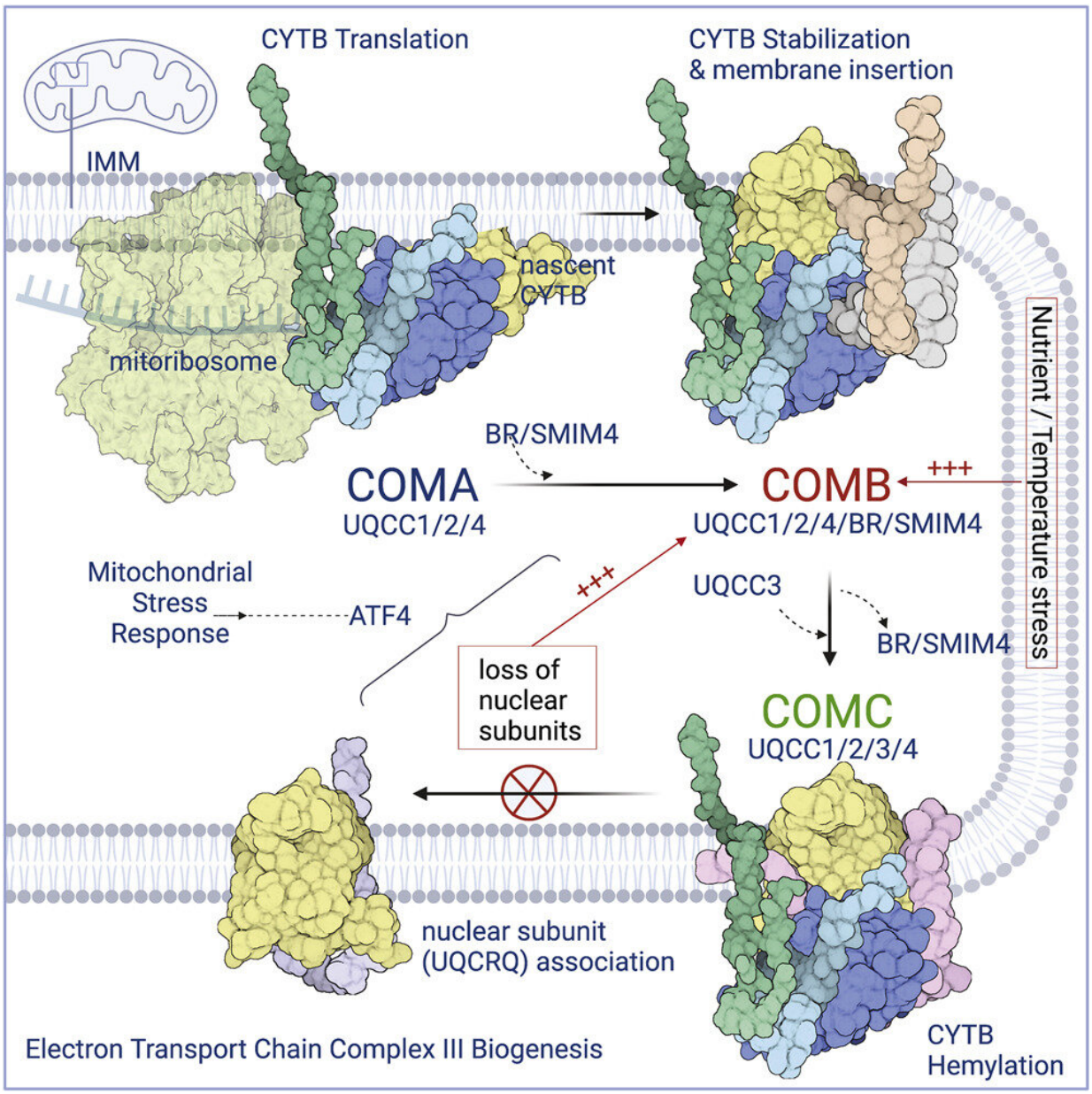

Graphical abstract. Credit: *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111204

Scientists at Duke-NUS Medical School have discovered new molecular details of how cells ensure that their energy supply is adjusted to meet energy demand. Their study, carried out in collaboration with researchers at the University of Melbourne in Australia and Duke University in Durham, North Carolina, U.S., highlights the crucial role microproteins play in assembling larger protein complexes inside energy-generating cell components known as mitochondria. Their results are published in *Cell Reports*.

Problems with mitochondria underlie a wide range of diseases, including common conditions such as heart failure, obesity, diabetes and cancer.

"Our long-term goal is to learn how to manipulate the microproteins we are investigating to combat mitochondrial dysfunction in patients," said senior author Assistant Professor Lena Ho, from Duke-NUS' Cardiovascular & Metabolic Disorders (CVMD) Program. "The more immediate significance of the research is to reveal new details of how mitochondria function and are maintained in all cells. The work could add an important new level of understanding to this central aspect of cell biology."

Mitochondria are bounded by a double membrane. The inner of the two membranes hosts a series of proteins that transfer electrons along what is called the electron transport chain. This electron transport is a crucial part of the processes that extract chemical energy from nutrients and ultimately store it in energy-rich molecules of adenosine triphosphate (ATP).

The new insight from the Duke-NUS team reveals that small microproteins (also called peptides) play a previously unrecognized role in allowing the electron transport chain to form. Specifically, they appear to work together to assist and control the assembly of one of the central proteins of the chain, called Complex III. This role allows the microproteins to participate in regulating the levels of electron transport chain proteins, and therefore energy supply, in response to changes in energy demand.

"Microproteins have fascinated but also mystified biologists from diverse fields for a long time," said Liang Chao, co-first author of the study, who is a Ph.D. candidate at Duke-NUS. "Our study provides an example of what they can do and how they participate in controlling energy metabolism at the deepest level of molecular detail."

"Mitochondria are the batteries and factories of our cells, making not only energy but also many of the building blocks required for cells to multiply and stay alive," said Dr. Shan Zhang, formerly a research fellow with Asst Prof Ho's Endogenous Peptides Lab, under Duke-NUS' CVMD Program, and now an Assistant Professor at Zhejiang University, China. "We clearly see that modulating the levels of these microproteins can lead to or protect against mitochondrial dysfunction, which is a feature that underlies almost all types of common diseases."

The team now plans to move on from these initial findings at the cellular level to more fully investigate the roles and significance of the microproteins in preclinical models and ultimately in humans.

"These next stages will hopefully lead us towards learning how to target the microprotein activity to treat mitochondrial diseases," Asst Prof Ho concluded.

"Innovations in health care and disease prevention benefit from advances

in knowledge made possible by fundamental scientific research, such as this study by Assistant Professor Ho and her team," said Professor Patrick Casey, senior vice-dean for research at Duke-NUS. "I look forward to seeing where the research leads us next."

More information: Chao Liang et al, Mitochondrial microproteins link metabolic cues to respiratory chain biogenesis, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111204

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