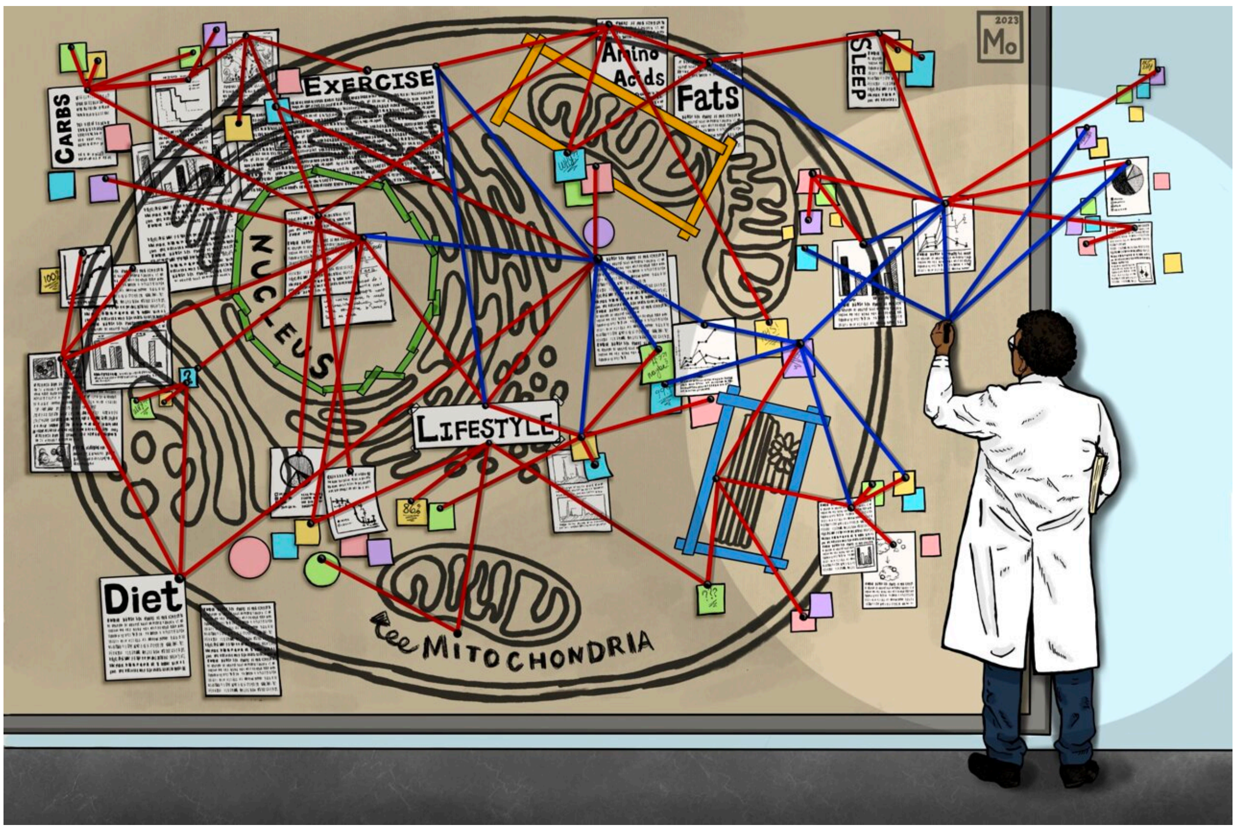
Biological network in cells helps body adapt to stresses on health

March 14 2023



Scientists are illuminating a a vast network of interactions that assist cells in adjusting in real time to withstand stresses on our health. Credit: Megan Okada for University of Utah Health

Every minute of every day, our body adapts to meet the needs of each moment. When we binge on carbs, exercise, or become sick, chemical reactions inside our cells switch on, slow down, or shift strategy so that we have the energy and strength we need.

All this happens without us knowing it, perhaps explaining why so little is understood about how the body senses and responds to these constant demands. Seeking answers to this question, scientists at University of Utah Health led research that opens up a whole new world within our cells. Their study, published in *Science*, uncovers a vast network of interactions that suggest how cells adjust in real time to withstand stresses on our health.

"We're discovering how nature has evolved to 'drug' its own proteins and pathways," says Jared Rutter, Ph.D., distinguished professor in the Department of Biochemistry at University of Utah and the study's corresponding author. "By following nature's lead, we're learning how to make better therapeutics."

These findings—and the technology that made them possible—has become the basis for the biotechnology company Atavistik Bio, co-founded by Rutter. The company is leveraging this new understanding to accelerate drug discovery for metabolic diseases and cancer.

At a more fundamental level, Rutter says, the advance deepens knowledge about how cells and our bodies work.

A New Frontier

The network described in the study represents an underappreciated layer of regulation in cells that comes from an unexpected source. For nearly 20 years, Rutter's lab has researched metabolism, the chemical reactions that produce energy and build essential components to keep cells running smoothly. Their new research finds that intermediate products of those chemical reactions are more than passive building blocks and sources of fuel for cells, as had long been thought.

Instead, these intermediate products, along with other metabolites, make up an expansive web of sentries that monitor the environment and prompt cells to adapt when needed. They do this by interacting with proteins and modifying how they work. Does a big meal pump too many carbs in the body? Or too much fat? Like a railroad switch that guides a train onto a new track, these protein-metabolite interactions shift metabolic operations to break down those nutrients and steady the course.

The study's first author Kevin Hicks, Ph.D., developed a new technology, termed MIDAS, that reveals the enormity of the regulatory network that acts as an interface between environmental cues and cell metabolism, called the protein-metabolite interactome. The highly sensitive technique identified interactions that had never been seen. An analysis of 33 human proteins involved in converting carbohydrates into fuel found 830 interactions with metabolites. Given that there are thousands of proteins in the cell, the full scale of the network is predicted to be much larger.

"It's surprising how little we know about the extent of these interactions," Hicks says. "We are pushing our understanding of the biological network in new directions."

Metabolic processes that become derailed can lead to illness and disease. Rutter and Hicks say that shedding light on additional interactions in the network will lead to a better understanding of root causes of diseases—and the development of new therapeutic approaches for getting things back on track.

The research published as "Protein-metabolite interactomics of carbohydrate metabolism reveal regulation of lactate dehydrogenase" and was a multi-institutional collaboration.

More information: Kevin G. Hicks et al, Protein-metabolite interactomics of carbohydrate metabolism reveals regulation of lactate dehydrogenase, *Science* (2023). DOI: 10.1126/science.abm3452. www.science.org/doi/10.1126/science.abm3452

Provided by University of Utah Health Sciences