Cracking the case of mitochondrial repair and replacement in metabolic stress

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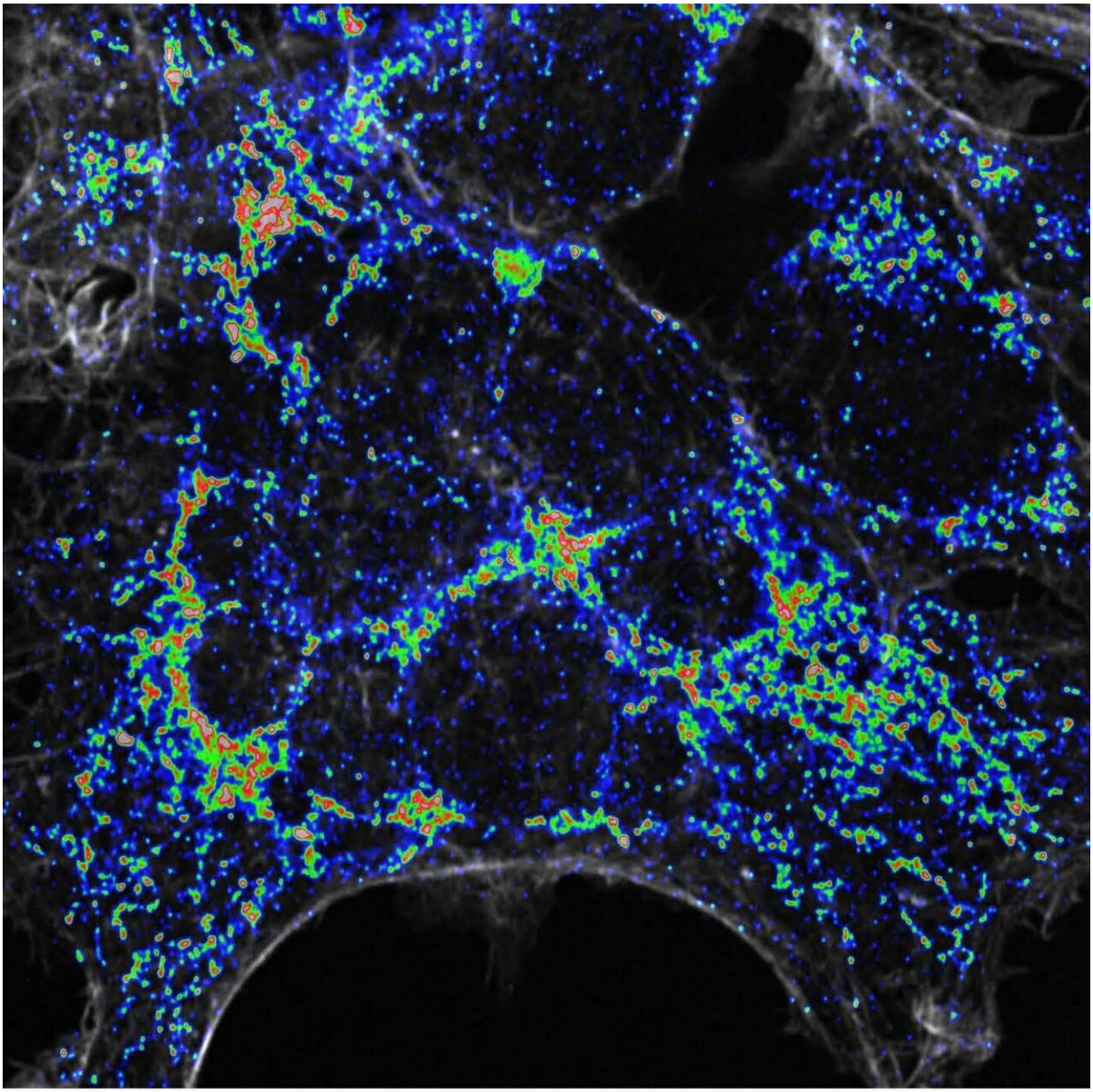

Mitochondria in the cell during metabolic stress. High increases in the number of mitochondria (red), medium increases (green), and low increases (blue). Credit: Salk Institute

Scientists often act as detectives, piecing together clues that alone may seem meaningless but together crack the case. Professor Reuben Shaw has spent nearly two decades piecing together such clues to understand the cellular response to metabolic stress, which occurs when cellular energy levels dip. Whether energy levels fall because the cell's powerhouses (mitochondria) are failing or due to a lack of necessary energy-making supplies, the response is the same: get rid of the damaged mitochondria and create new ones.

Now, in a study published in *Science* on April 20, 2023, Shaw and team cracked the case on this process of removal and replacement. It turns out that a protein called FNIP1 is the critical link between a cell sensing low energy levels and eliminating and replacing damaged mitochondria.

"This is a final puzzle piece that connects decades of studies from labs all over the world. It solves one of the final mysteries about how the signal to make new mitochondria is tied to the original signal that energy levels are low," says Shaw, senior author and director of Salk's Cancer Center. "This discovery that FNIP1 is at the heart of the metabolic stress response will help us understand healthy aging, cancerous tumors, neurodegenerative diseases, and so much more. This is a fundamental cellular process that ties into many diseases and will be in textbooks for years to come."

Nearly 15 years ago, Shaw's lab discovered that an enzyme called AMPK was responsible for starting the removal process of damaged mitochondria. Later, the team showed that a part of this removal process

is the cell breaking damaged mitochondria into hundreds of fragments, then sorting through those fragments to remove the damaged parts and repurpose the functional parts. But the question remained—how is the repair of damaged powerhouses connected to the signal to start making new powerhouses from scratch?

When mitochondria are damaged, or when sugar (glucose) or oxygen levels fall in the cell, energy levels quickly fall. After an energy decrease as small as 10 percent, AMPK is triggered. AMPK communicates with another protein, called TFEB, to instruct genes to make 1) lysosomes (cellular recycling centers) to remove damaged mitochondria, and 2) replacement mitochondria. But how AMPK and TFEB communicated was unclear.

When a new suspect, FNIP1, joined in on the metabolic stress mystery, the answer was finally within reach. FNIP1 is the most recently discovered protein of the AMPK, TFEB, FNIP1 trio. For years, researchers were only able to connect FNIP1 to AMPK, and thus thought it may be a throwaway clue or a red herring—instead, it was the clue that cracked the case.

"Many years ago, we suspected the FNIP1 protein might be important for AMPK-TFEB communication that led to mitochondria synthesis and replacement in the cell during metabolic stress, but we didn't know how FNIP1 was involved," says first author Nazma Malik, a postdoctoral fellow in Shaw's lab. "If correct, this finding would finally link AMPK and TFEB, which would both enrich our understanding of metabolism and cellular communication and provide a novel target for therapeutics."

To determine whether FNIP1 was the missing link between AMPK and TFEB, the researchers compared unaltered human kidney cells with two altered types of human kidney cells: one that lacked AMPK entirely, and another that lacked only the specific parts of FNIP1 that AMPK talks to.

The team discovered that AMPK signals FNIP1, which then opens the gate to let TFEB into the nucleus of the cell. Without FNIP1 receiving the signal from AMPK, TFEB remains trapped outside the nucleus, and the entire process of breaking down and replacing damaged mitochondria is not possible. And without this robust response to metabolic stress, our bodies—along with the many plants and animals whose cells also rely on mitochondria—would not be able to function effectively.

"Watching this project evolve over the last 15 years has been a rewarding experience," says Shaw, holder of the William R. Brody Chair. "I am proud of my dedicated, talented team, and I cannot wait to see how this monumental finding will influence future research—at Salk and beyond."

More information: Nazma Malik et al, Induction of lyosomal and mitochondrial biogenesis by AMPK phosphorylation of FNIP1, *Science* (2023). DOI: 10.1126/science.abj5559.
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Provided by Salk Institute

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