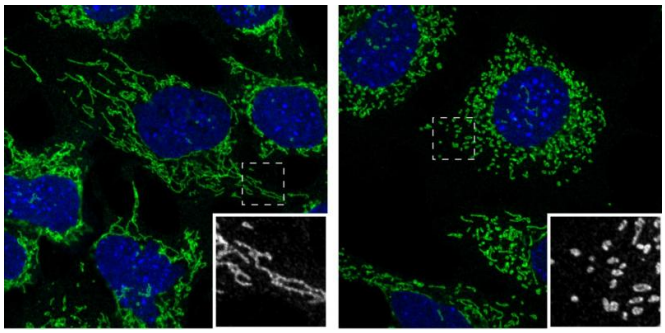
How the cell's power station survives attacks

14 January 2016



Scientists at the Salk Institute demonstrated how a molecular sensor detects damage in mitochondria (green) and induces reorganization of the entire mitochondrial network (nuclei in blue). Normal mitochondria (left) undergo massive reorganization (right) after exposure to the toxin rotenone. Credit: Salk Institute

Mitochondria, the power generators in our cells, are essential for life. When they are under attack—from poisons, environmental stress or genetic mutations—cells wrench these power stations apart, strip out the damaged pieces and reassemble them into usable mitochondria.

Now, scientists at the Salk Institute have uncovered an unexpected way in which cells trigger this critical response to threats, offering insight into disorders such as mitochondrial disease, cancer, diabetes and neurodegenerative disease—particularly Parkinson's disease, which is linked to dysfunctional mitochondria. The work appears January 15, 2016 in *Science*.

"Outside marauders come into these power stations of the cell—the mitochondria—and in response, the power stations break into smaller fragments," says Reuben Shaw, senior author and Salk professor in the Molecular and Cell Biology Laboratory.

In an average human cell, anywhere from 100 to 500 mitochondria churn out energy in the form of ATP molecules, which act like batteries to carry power to the rest of the cell. At any given time, one or two mitochondria fragment (fission) or reform (fusion) to cycle out any damaged parts. But when a poison—like cyanide or arsenic—or other dangers threaten the mitochondria, a mass fragmentation takes place.

Researchers have known for years that mitochondria undergo this fragmentation when treated with drugs that affect the mitochondria, but the biochemical details of how the mitochondria damage is sensed and how that triggers the rapid fission response has not been clear until now.

In the new work, the Salk team found that when cells are exposed to mitochondria damage, a central cellular fuel gauge, the enzyme AMPK, sends an emergency alert to mitochondria instructing them to break apart into many tiny mitochondrial fragments. Interestingly, AMPK is activated by the widely used diabetes therapeutic metformin, as well as exercise and a restricted diet. The new findings suggest that some of the benefits from these therapies may result from their effects in promoting mitochondrial health.

Prior research by Shaw's group and others had uncovered AMPK's role in helping to recycle damaged mitochondrial pieces as well as signaling to the cell to make new mitochondria. But this new role of rapidly triggering mitochondrial fragmentation "really places AMPK at the heart of mitochondria health and long-term well-being," says Shaw, who is also holder of the William R. Brody Chair.

To uncover exactly what happens in those first few minutes, the team used the gene editing technique CRISPR to delete AMPK in cells and showed that, even when poison or other threats are introduced to the mitochondria, they do not fragment without

AMPK. This indicates that AMPK somehow directly acts on mitochondria to induce fragmentation.

The group then looked at a way to chemically turn on AMPK without sending attacks to mitochondria. To their surprise, they found that activating AMPK alone was enough to cause the mitochondria to fragment, even without the damage.

"I could not believe how black and white the results were. Just turning on AMPK by itself gives you as much fragmentation as a mitochondrial poison," says Shaw.

The team discovered why this was: when the cell's power stations are disrupted, the amount of energy floating around a cell—ATP—is lowered. After just a few minutes, AMPK detects this reduction of energy in the cell and hurries to the mitochondria. Like a guard pulling a fire alarm, AMPK activates a receptor on the outside membrane of a mitochondrion to signal it to fragment.

Drilling down further, the researchers found that AMPK actually acts on two areas of a mitochondrial receptor, called mitochondrial fission factor (MFF), to start the process. MFF calls over a protein, Drp1, that binds and wraps around the mitochondrion like a beaded noose to twist and break it apart.

"We discovered that the modification of MFF by AMPK is needed for MFF to call over more Drp1 to the mitochondria," says Erin Quan Toyama, one of the first authors of the paper and a Salk research associate. "Without AMPK sending the alarm, MFF cannot call over to Drp1 and there is no new fragmentation of mitochondria after damage."

In the future, the team is interested in addressing what other consequences this signaling pathway has for specific cell types, according to Sébastien Herzig, the other first author of the paper and a Salk research associate. "We want to see what a defect in communication between the mitochondria and AMPK would do to different tissues, particularly ones very dependent on healthy mitochondria, such as brain, muscle and heart," says Herzig.

Adds Toyama, "On one hand, AMPK is known to be important for type 2 diabetes, immune disease and cancer. On the other hand, mitochondrial dysfunction is becoming increasing connected to metabolic diseases and neurodegenerative diseases. We're making some of the first steps in connecting these two things that have major disease implications."

More information: "AMP-activated protein kinase mediates mitochondrial fission in response to energy stress" www.sciencemag.org/lookup/doi/ … 1126/science.aab4138

Provided by Salk Institute