Cell death pathway linked to mitochondrial fusion

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New research led by UC Davis scientists provides insight into why some body organs are more susceptible to cell death than others and could eventually lead to advances in treating or preventing heart attack or stroke.

In a paper published Jan. 21 in the journal *Molecular Cell*, the UC Davis team and their collaborators at the National Institutes of Health and Johns Hopkins University report that Bax, a factor known to promote cell death, is also involved in regulating the behavior of mitochondria, the structures that provide energy inside living cells.

Mitochondria constantly split and fuse. The proteins that control the splitting of mitochondria also promote a process called apoptosis, or programmed cell death. In contrast, the proteins that control mitochondrial fusion help protect against cell death. Cell death can happen when cells are starved of oxygen, for example during a heart attack or stroke.

Yeast have a single protein that controls outer membrane fusion, but both human and mouse cells have two proteins, called MFN1 and MFN2, which control outer membrane fusion. Using mitochondria from cells derived from genetically modified "knockout" mice, Suzanne Hoppins, a postdoctoral researcher at UC Davis, and Jodi Nunnari, a professor of molecular cell biology, studied how these two proteins work together and the role specific genes play in that process.

The research team discovered that these proteins combine with themselves or each other to form a tether between two mitochondria, leading to fusion. All three combinations -- MFN1/MFN1, MFN1/MFN2 and MFN2/MFN2 -- can promote membrane fusion, but the combination of MFN1/MFN2 is by far the most efficient, Hoppins said.

Hoppins also found that a soluble form of Bax, a protein that triggers apoptosis, can also stimulate mitochondria to fuse. It acts only through the MFN2/MFN2 combination, she found.

The form of Bax that promotes mitochondrial fusion is different from the type that leads to cell death, Nunnari said. Bax leads to cell death when it inserts itself in the mitochondrial membrane. In its soluble, free-floating form, it causes mitochondria to fuse instead.

MFN1 and MFN2 are found in different amounts in different body organs. MFN2 is more abundant in the brain and heart -- tissues where cell death can have disastrous consequences.

The paper shows how MFN2 could act to protect the brain or heart from cell death, by using Bax in a different form, Nunnari said.

"This shows that the fusion machine is both positively and negatively regulated in cells and opens doors to finding the regulatory mechanisms and discovering ways to increase or decrease the sensitivity of cells to apoptosis," Hoppins said. That could lead to new drugs that save cells, for heart disease and stroke, or that kill cells, for cancer.

Provided by University of California - Davis