Mitochondrial metabolic regulator SIRT4 guards against DNA damage

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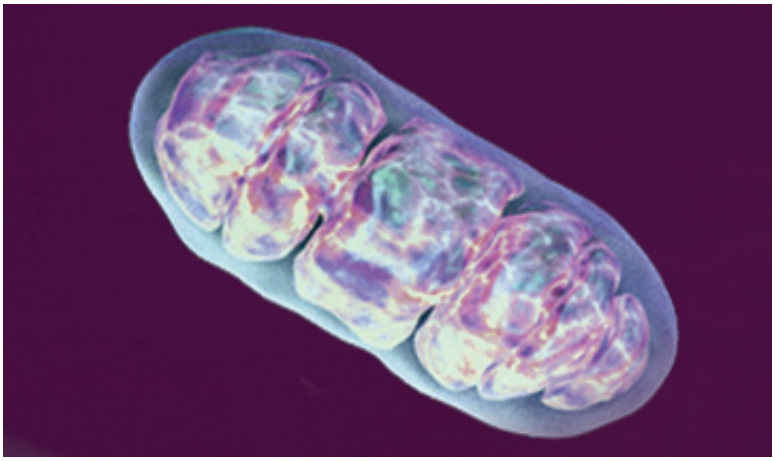

A healthy mitochondrion contains the metabolic regulator SIRT4, which responds to DNA damage and other stress. Credit: National Institute on Aging

(Medical Xpress)—Healthy cells don't just happen. As they grow and divide, they need checks and balances to ensure they function properly while adapting to changing conditions around them.

Researchers studying a set of proteins that regulate physiology, caloric restriction and aging have discovered another important role that one of them plays. SIRT4, one of seven sirtuin proteins, is known for controlling fuel usage from its post in the mitochondria, the cell's energy source. It responds to stressful changes in the availability of nutrients for the cell.

New research reveals that SIRT4 is also extremely sensitive to a different form of stress: DNA damage. This unsuspected response by the metabolic checkpoint means SIRT4 doubles as a sentry guarding against cancer, which is spurred by genetic abnormalities.

Sirtuins have become familiar for their connection to longevity and to resveratrol, the red-wine compound that activates SIRT1, but less attention has been focused on SIRT3, SIRT 4 and SIRT5, all of which are found in mitochondria. Marcia Haigis, HMS associate professor of cell biology, led a team that has uncovered SIRT4 as an important player in the DNA damage response pathway, coordinating a sequence of events that normally result[s] in tumor suppression. They published their results April 4 in *Cancer Cell*.

"When we started studying SIRT4, we were focused only on its metabolic role, looking for functions related to diabetes and obesity," said Haigis. "What we found, to our surprise, was that SIRT4 was responsive to DNA damage, so that led us to investigate the metabolic response to DNA damage and how SIRT4 controls the metabolic response to genotoxic stress."

To see how SIRT4 normally functions, Haigis and her colleagues induced DNA damage by exposing cells in a lab dish to ultraviolet light. This damage triggered a halt in glutamine metabolism, limiting the amount of nutrients the cell could use as it goes through a cycle of division and growth.

Blocking the cell cycle at this juncture is important. If cell growth after DNA damage goes unchecked, proliferation of impaired cells can lead to cancer. When SIRT4 works properly, this chain of events is broken before bad cells and their abnormal genes multiply. SIRT4 blocks glutamine metabolism, arrests the cell cycle and suppresses tumor formation.

The scientists tested this SIRT4 response in mice. Bred to lack the gene that encodes the SIRT4 protein but otherwise normal, the mice spontaneously developed lung cancer by 15 months.

"When SIRT4 is missing, you don't have this metabolic checkpoint involving glutamine, which is important because glutamine is an amino acid required for proliferation in the cell," Haigis said. "Without SIRT4, the cell keeps dividing even in the face of DNA damage, so the cell accumulates more damage."

The scientists also analyzed data showing SIRT4 gene expression levels are low in several human cancers, including small-cell lung carcinoma, gastric cancer, bladder carcinoma, breast cancer and leukemia.

While they cannot say if SIRT4 loss alone will initiate cancer, its absence appears to create an environment in which tumor cells survive and grow.

"Our findings suggest that SIRT4 may be a potential target against tumors," they conclude.

More information: Jeong, S. et al. SIRT4 Has Tumor-Suppressive Activity and Regulates the Cellular Metabolic Response to DNA Damage by Inhibiting Mitochondrial Glutamine Metabolism, *Cancer Cell*, April 4, 2013. www.cell.com/cancer-cell/abstract/S1535-6108%2813%2900078-0

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