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'Rewired' mice show signs of longer lives with fewer age-related illnesses

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While developing a new cancer drug, researchers at The Wistar Institute discovered that mice lacking a specific protein live longer lives with fewer age-related illnesses. The mice, which lack the TRAP-1 protein, demonstrated less age related tissue degeneration, obesity, and spontaneous tumor formation when compared to normal mice. Their findings could change how scientists view the metabolic networks within cells.

In healthy cells, TRAP-1 is an important regulator of metabolism and has been shown to regulate energy production in mitochondria, organelles that generate chemically useful energy for the cell. In the mitochondria of cancer cells, TRAP-1 is universally overproduced.

The Wistar team's report, which appears in the journal *Cell Reports* (available online now), shows how "knockout" mice bred to lack the TRAP-1 protein compensate for this loss by switching to alternative cellular mechanisms for making energy.

"We see this astounding change in TRAP-1 knockout mice, where they show fewer signs of aging and are less likely to develop cancers," said Dario C. Altieri. M.D., Robert and Penny Fox Distinguished Professor and director of The Wistar Institute's National Cancer Institute-designated Cancer Center. "Our findings provide an unexpected explanation for how TRAP-1 and related proteins regulate metabolism within our cells."

"We usually link the reprogramming of metabolic pathways with human diseases, such as cancer," Altieri said. "What we didn't expect to see were healthier mice with fewer tumors."

Altieri and his colleagues created the TRAP-1 knockout mice as part of their ongoing investigation into their novel drug, Gamitrinib, which targets the protein in the mitochondria of tumor cells. TRAP-1 is a member of the heat shock 90 (HSP90) protein family, which are "chaperone" proteins that guide the physical formation of other proteins and serve a regulatory function within mitochondria. Tumors use HSP90 proteins, like TRAP-1, to help survive therapeutic attack.

"In tumors, the loss of TRAP-1 is devastating, triggering a host of catastrophic defects, including metabolic problems that ultimately result in in death of the tumor cells," Altieri said. "Mice that lack TRAP-1 from the start, however, have three weeks in the womb to compensate for the loss of the protein."

The researchers found that in their knockout mice, the loss of TRAP-1 causes mitochondrial proteins to misfold, which then triggers a compensatory response that causes cells to consume more oxygen and metabolize more sugar. This causes mitochondria in knockout mice to produce deregulated levels of ATP, the chemical used as an energy source to power all the everyday molecular reactions that allow a cell to function.

This increased mitochondrial activity actually creates a moderate boost in oxidative stress ("free radical damage") and the associated DNA damage. While DNA damage may seem counterproductive to longevity and good health, the low level of DNA damage actually reduces cell proliferation—slowing growth down to allow the cell's natural repair mechanisms to take effect.

According to Altieri, their observations provide a mechanistic foundation for the role of chaperone molecules, like HSP90, in the regulation of bioenergetics in mitochondria—how cells produce and use the chemical energy they need to survive and grow. Their results explain some contradictory findings in the scientific literature regarding the regulation of bioenergetics and dramatically show how compensatory mechanisms can arise when these chaperone molecules are taken out of the equation.

"Our findings strengthen the case for targeting HSP90 in tumor cells, but it also opens up a fascinating array of questions that may have implications for metabolism and longevity," Altieri said. "I predict that the TRAP-1 knockout mice will be a valuable tool for answering these questions."

Provided by The Wistar Institute