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More evidence for longevity pathway

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New research reinforces the claim that resveratrol—a compound found in plants and food groups, notably red wine—prolongs lifespan and health-span by boosting the activity of mitochondria, the cell's energy supplier.

"The results were surprisingly clear," said David Sinclair, a professor of genetics at Harvard Medical School and the study's senior author. "Without the mitochondria-boosting gene SIRT1, resveratrol does not work."

The findings are to be published May 1 in the journal *Cell* Metabolism.

Over the last decade, Sinclair and colleagues including Leonard Guarente at Massachusetts Institute of Technology have published a body of research describing how resveratrol improves energy production and overall health in cells by activating a class of genes called sirtuins that are integral to mitochondrial function. The cell's power supplier, mitochondria are essential not just for longevity but for overall health.

Sinclair and colleagues had studied sirtuins in a variety of model organisms: yeast, worms, flies and mice. For the first three organisms they were able to thoroughly knock out SIRT1 and show that cells lacking the gene don't respond to resveratrol. But no one had been able to demonstrate the effect in mice, which die at birth without the SIRT1 gene.

In order to solve this obstacle, Nathan Price and Ana Gomes, graduate

students in the Sinclair lab, spent three years engineering a new mouse model. These mice, seemingly normal in every way, were designed so that SIRT1 would systemically switch off when the mice were given the drug Tamoxifen.

"This is a drug inducible, whole body deletion of a gene," said Sinclair. "This is something that's rarely been done so efficiently. Moving forward, this mouse model will be valuable to many different labs for other areas of research."

The results were plain: when mice were given low doses of resveratrol after SIRT1 was disabled, the researchers found no discernable improvement in mitochondrial function. In contrast, the mice with normal SIRT1 function given resveratrol showed dramatic increases in energy.

While the tantalizing prospect of increasing healthy lifespan has made resveratrol the subject of intense scientific interest, some researchers have questioned the link to SIRT1. A competing theory holds that resveratrol may work by activating a separate energy pathway called AMPK, which, while also related to mitochondria, does not involve sirtuin genes.

In their new paper, Sinclair and colleagues report that when mice lacking SIRT1 were given low doses of resveratrol, AMPK was unaffected. When doses were significantly increased in these mice, AMPK was activated, but still no benefit to mitochondrial function resulted.

"Resveratrol is a dirty molecule, so when you give very, very high doses, many things could be happening," said Sinclair. "It's standard when you study molecules that you use the lowest dose that gives you an effect because of the risk of hitting other things if you use too much. But for the downstream benefits on energy, you still need SIRT1. Our paper

shows that SIRT1 is front and center for any dose of resveratrol."

More information: *Cell Metabolism*, May, 2012, Vol 15, No 5

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