

## Science News

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### **Resveratrol: Study Resolves Controversy On Life-Extending Red Wine Ingredient, Restores Hope for Anti-Aging Pill**

*May 1, 2012* — A study in the May issue of the Cell Press journal *Cell Metabolism* appears to offer vindication for an approach to anti-aging drugs that has been at the center of heated scientific debate in recent years. The new findings show for the first time that the metabolic benefits of the red wine ingredient known as resveratrol evaporate in mice that lack the famed longevity gene SIRT1.

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"Resveratrol improves the health of mice on a high-fat diet and increases life span," said David Sinclair of Harvard Medical School. The question was how. Resveratrol is a dirty molecule, he explained. Its benefits had been attributed largely to its actions on SIRT1, based on studies in yeast, worms, and flies, but the naturally occurring ingredient has other effects; it influences dozens of proteins, and some evidence had pointed to the importance of another well-known gene (called AMPK) for resveratrol's metabolic benefits. That called into question not only the biology, but also whether SIRT1-targeted drugs in development were aimed in the wrong direction. (Those doubts and other factors led the pharmaceutical company Sirtris to halt its last clinical trial of resveratrol last year.)

Answers were hard to come by in mice, because animals lacking SIRT1 altogether don't survive. Sinclair and his colleagues have now overcome that obstacle by producing mice in which the SIRT1 gene can be completely turned off in adults. They've discovered that those SIRT1-deficient adult mice don't enjoy the benefits of resveratrol.

The study also provides insight into another important aspect of the resveratrol controversy. Doubts had arisen in part because the red wine ingredient seems to act in different ways at different doses. The study by Sinclair and colleagues clears those details up, too.

They show that resveratrol targets SIRT1 directly at moderate doses and hits other targets at higher ones. Importantly, SIRT1 is required for resveratrol's benefits irrespective of dose. Based on the findings, Sinclair emphasizes the value of finding the lowest effective dose of resveratrol, and perhaps any drug, to avoid off-target effects.

George Vlasuk, CEO of Sirtris, who was not involved in the new study, says the findings in *Cell Metabolism* offer the "first definitive evidence" for a direct link between SIRT1 and the metabolic benefits of resveratrol.

"The work by Price et al. strongly supports the basic rationale being pursued at Sirtris, which focuses on the development of small-molecule compounds that directly activate the enzymatic activity of SIRT1 as a new therapeutic approach to many diseases of aging," Vlasuk wrote in an email.

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