New study uncovers probable mechanism underlying resveratrol activity

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National Institutes of Health researchers and their colleagues have identified how resveratrol, a naturally occurring chemical found in red wine and other plant products, may confer its health benefits. The authors present evidence that resveratrol does not directly activate sirtuin 1, a protein associated with aging. Rather, the authors found that resveratrol inhibits certain types of proteins known as phosphodiesterases (PDEs), enzymes that help regulate cell energy.

These findings may help settle the debate regarding resveratrol's biochemistry and pave the way for resveratrol-based medicines. The chemical has received significant interest from pharmaceutical companies for its potential to combat diabetes, inflammation, and cancer. The study appears in the Feb. 3 issue of *Cell*.

"Resveratrol has potential as a therapy for diverse diseases such as type 2 diabetes, Alzheimer's disease, and heart disease," said lead study author Jay H. Chung, M.D., Ph.D., chief of the Laboratory of Obesity and Aging Research at the NIH's National Heart, Lung, and Blood Institute. "However, before researchers can transform resveratrol into a safe and effective medicine, they need to know exactly what it targets in cells."

Several previous studies suggested that resveratrol's primary target is sirtuin 1. Chung and colleagues suspected otherwise when they found that resveratrol activity required another protein called AMPK. This would not be the case if resveratrol directly interacted with sirtuin 1.

In this study, the researchers methodically traced out the metabolic activity in cells treated with resveratrol and identified PDE4 in the skeletal muscle as the principal target for the health benefits of resveratrol. By inhibiting PDE4, resveratrol triggers a series of events in a cell, one of which indirectly activates sirtuin 1.

To confirm that resveratrol attaches to and inhibits PDE proteins, Chung's group gave mice rolipram, a drug known to inhibit PDE4. Rolipram reproduced all of the biochemical effects and health benefits of resveratrol, such as preventing diet-induced obesity, improving glucose tolerance, and increasing physical endurance.

Chung noted that because resveratrol in its natural form interacts with many proteins, not just PDEs, it may cause not-yet-known toxicities as a medicine, particularly with long-term use. He added that the levels of resveratrol found in wine or foods are likely not high enough to produce significant health benefits or problems. Convincing clinical studies in humans have used about 1 gm of resveratrol per day, roughly equal to the amount found in 667 bottles of red wine.

The study results also suggest that inhibitors of PDE4 may offer the benefits of resveratrol without the potential toxicities arising from resveratrol's interactions with other proteins. One PDE4 inhibitor called roflumilast has already been approved by the FDA for the treatment of COPD (chronic obstructive pulmonary disease).

"This result underscores the need for careful, well-controlled studies to illuminate how these natural products operate," said Robert Balaban, Ph.D., director of the NHLBI Division of Intramural Research. "As Dr. Chung's work suggests, the effects of resveratrol seem to be more complicated than originally thought. However, this new insight into the phosphodiesterases might prove an interesting avenue to pursue."

In addition to Dr. Chung's lab at the NHLBI, other contributors to this study included collaborators in the Cardiovascular Pulmonary Branch of the NHLBI; the University of California, Davis; the University of North Carolina, Chapel Hill; University of Texas Southwestern Medical Center, Dallas; Sun Yat-sen University, Guangzhou, China; University Medical Center, Utrecht, The Netherlands; and Emerald BioStructures, Bainbridge Island, Wash.

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