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Questions hang over red-wine chemical

How resveratrol benefits health a matter of debate.

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Resveratrol, which is found in red wine, can lengthen life and prevent diabetes in some organisms, but how remains controversial.

Mice fed the chemical resveratrol are impervious to the harmful effects of a high-fat diet, but the mechanism underlying this phenomenon is the subject of some controversy. An explanation published today in *Cell* differs from that given by earlier research, raising questions about ongoing efforts to develop medicines that mimic the chemical[1].

Resveratrol is made by many plants, but is most often associated with red wine, and the skins of red grapes are rich in it. The chemical gained international attention after scientists discovered that it activates a pathway that seems to lengthen lifespan in some organisms[2] and, later, that mice that consume resveratrol can eat a high-calorie diet without gaining weight or developing diabetes[3, 4].

Some of the researchers who reported resveratrol's beneficial effects founded a biotechnology company called Sirtris with the goal of battling age-related diseases such as diabetes. In 2008, the London-based drug company GlaxoSmithKline paid US$720 million for Sirtris. The company is named after proteins called sirtuins, which have important roles in ageing, and Sirtris' founders contended that resveratrol works, in part, by activating a sirtuin called Sirt1.

However, a number of scientists have since challenged this means of action, arguing that resveratrol does not activate Sirt1 directly and that the previous results were an artefact of the test used to measure the protein[5]. If this is true, it could complicate efforts to identify and improve drugs intended to work in the same way as resveratrol.

The missing link

Jay Chung, an endocrinologist at the National Heart Lung and Blood Institute in Bethesda, Maryland, who led the *Cell* study, focused on another enzyme, AMPK, that is activated both when cells are starved of energy and when mice are given resveratrol. Chung knew that resveratrol does not directly trigger AMPK, so he and his team set out to find the missing links.

Their search identified a series of proteins controlled by a messenger chemical called cyclic AMP (cAMP). This molecule is one of the first produced when cells are low on energy, and Chung's team found that resveratrol does not trigger AMPK when these messenger molecules are blocked.

The authors showed that resveratrol boosts cAMP levels by blocking enzymes called phosphodiesterases that break it down. When they gave mice a drug that inhibits the phosphodiesterase that is most abundant in muscle cells, the rodents responded as if they were on resveratrol. They did not gain weight or develop diabetes while on a high-fat diet, and their muscles expressed many of the genes that are triggered by resveratrol.

"I think this paper is a major advance for the field," says molecular biologist Joseph Baur at the University of Pennsylvania in Philadelphia, adding that the work fills in many of the biochemical details of resveratrol's effects. However, Matt Kaeberlein, a biochemist at the University of Washington in Seattle, believes that the chemical triggers still more biological pathways to achieve its effects on health. "I'll be shocked if there aren't other targets of resveratrol," he says.

Sirtris halted the development of drugs based on resveratrol in 2010 because of its side effects, but is continuing to pursue similar compounds. Chung says that these molecules may also work by blocking phosphodiesterases rather than by activating Sirt1 directly. But Sirtris's chief executive George Vlasuk questions whether resveratrol works by blocking phosphodiesterases. He says the drug Chung's team gave the mice is far more potent than resveratrol at blocking the enzymes, and it is therefore not accurate to assume they prevent diabetes and obesity in the same manner.

Vlasuk adds that Sirtris concluded a long time ago that their other drugs do not work by blocking phosphodiesterases, and he says they have no plans to repeat Chung's experiments.

Regulators recently approved a drug that inhibits a phosphodiesterase produced in muscle cells for the treatment of chronic obstructive pulmonary disease, and Chung hopes to conduct a clinical trial examining its effects on patients who are at risk of developing type 2 diabetes.

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