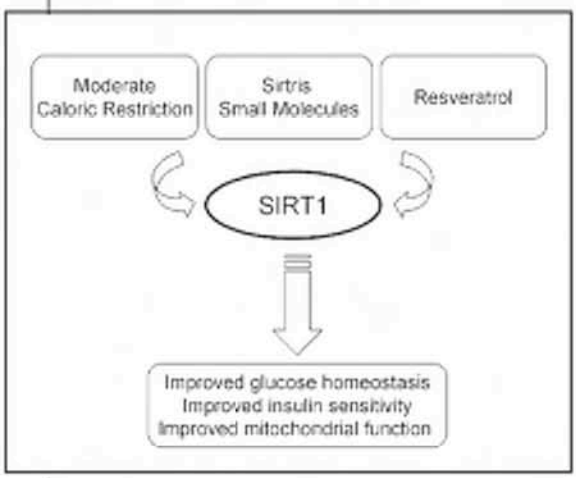
Novel Molecules Activate the SIRT1 Fountain of Youth

By Michelle Jung

Recent research has shown that restricting caloric intake by 20-40% may significantly increase one's life span. Although this data has not been confirmed in humans, moderately reducing the number of calories consumed decreased many signs of aging in monkeys, mice, worms, and yeast (1). Caloric restriction activates the protein SIRT1, which is critical for realizing the diet's health benefits. Previously, it was known that the molecule resveratrol, naturally found in red wine, also activated SIRT1 (2). Recently, researchers at Sirtris Pharmaceuticals, the University of California San Diego, and Harvard Medical School discovered several small molecules that also activate SIRT1 and are a thousand times more powerful than resveratrol (2).



▲ Small molecules discovered activate SIRT1 and provide similar health benefits as moderate caloric restriction and resveratrol.

The nuclear protein SIRT1, a member of the Sirtuin family of enzymes, is a deacetylase that is dependent on nicotinamide adenine dinucleotide (NAD+) (3). NAD+ is a key energy molecule involved in many metabolic processes, including the breakdown of glucose. Researchers are still trying to understand the different biological roles of SIRT1, but the protein is known to be upstream of the tumor suppressor protein p53. In fact, SIRT1 deacetylates p53, inhibiting its expression (4).

The newly discovered small molecules activate SIRT1 by increasing its functionality. In the presence of these novel molecules, less substrate is required to activate SIRT1. Specifically, these compounds bind to an allosteric site on SIRT1 to decrease KM, the Michaelis constant, for deacetylation reactions. The Michaelis constant is a measure of the amount of substrate required to achieve half the maximum reaction rate for a specific enzyme-substrate reaction (4).

As expected, the activation of SIRT1 by these small molecules resulted in an indirect increase in p53 deacetylation. Furthermore, researchers saw that these molecules could improve glucose homeostasis, insulin sensitivity, and mitochondrial function in several insulin-resistant animal models including diet-induced obese mice. These results indicated that, by activating SIRT1, the new compounds were able to provide similar health benefits to resveratrol (4).

A major criticism of caloric restriction studies is the practical implication of such work. Although scientific data may back up the hypothesis that caloric restriction can provide certain health benefits, humans may have difficulties implementing this regimen into their lifestyles. Dr. Jay Phelan of the University of California, Los Angeles, notes: "Caloric restriction is doomed to fail, and will make people miserable in the process of attempting it" (5). From that perspective, these novel SIRT1 activators may be an easier, but pricier alternative to caloric restriction diets. Pharmaceutical companies, like Sirtris, are seeking to develop drugs like the newly discovered small molecules that can activate SIRT1. However, the potential side-effects of activating SIRT1 are still being determined.

Although SIRT1 is known to be a tumor suppressor, certain cancers are characterized by an increase in SIRT1 activity (6). Therefore, whether or not these new compounds will be safe for extended use in humans is still unknown. Until these details are determined, the promise of longevity in a bottle will remain as elusive as before. H

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