SIRT3 in Calorie Restriction: Can You Hear Me Now?

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Caloric restriction decreases oxidative damage and extends life span in many organisms. Someya et al. (2010) show that the sirtuin SIRT3 mediates the protective effects of caloric restriction on age-related hearing loss by promoting the mitochondrial antioxidant system through the regulation of isocitrate dehydrogenase 2 (Idh2).

Despite two decades of effort, caloric restriction remains the only treatment demonstrated to extend life span and to delay the progression of several diseases normally associated with aging, such as cancer, diabetes, and neurological disorders. Early experiments in yeast showed that the life span extension mediated by caloric restriction involves Sir2, the founding member of the sirtuin family of histone deacetylases. However, later experiments have questioned this association (Longo and Kennedy, 2006), and the role of mammalian sirtuins in life span extension by caloric restriction is still under study. In this context, although SIRT1 appears to be the major mammalian sirtuin involved in the metabolic effects of caloric restriction (Haigis and Guarente, 2006), the precise role of sirtuins in the longevity response remains unclear. In this issue of *Cell*, Someya et al. (2010) bring some light to the field by describing a new function for the mitochondrial SIRT3 protein in the prevention of hearing loss mediated by caloric restriction during aging. These tantalizing results suggest that SIRT3 might play an important role in slowing the aging process in mammals.

Age-related hearing loss is a hallmark of mammalian aging and the most common sensory disorder in the elderly (Liu and Yan, 2007). It is characterized by a gradual loss of spiral ganglion neurons and sensory hair cells in the cochlea of the inner ear (Liu and Yan, 2007). Given that the affected cells are postmitotic and do not regenerate, their loss leads to an age-associated decline in hearing function. Several groups have studied hearing loss as an example of age-related degeneration in mouse models. Remarkably, early work demonstrated that caloric restriction slows age-related hearing loss in animal models (Sweet et al., 1988). Moreover, in their previous work, Prolla and colleagues demonstrated that caloric restriction induces expression of the SIRT3 gene in the cochlea (Someya et al., 2007). They now elegantly follow up on these results, proving a role for this sirtuin in the delay in hearing loss due to caloric restriction and elucidating the molecular mechanisms underlying this effect.

Someya et al. use wild-type and SIRT3-deficient mice fed a diet in which caloric intake is reduced to 75% and compare them to control mice fed with a regular diet. The authors first look at the hearing response of the animals and find that, as expected, aging leads to hearing loss in both wild-type and SIRT3-deficient mice. However, whereas caloric restriction delays the progression of hearing loss in wild-type mice, this effect is completely abolished in SIRT3-deficient animals. These results are consistent with the effects of caloric restriction on spiral ganglion neurons and hair cells in these mice. In wild-type animals, a calorie restricted diet reduces the age-related loss of neurons and hair cells, whereas this effect is abrogated in SIRT3-deficient mice. Together, these results clearly pinpoint SIRT3 as a critical molecular determinant regulating the response to caloric restriction in age-related hearing loss.

The authors next study the metabolic effects induced by caloric restriction in SIRT3-deficient mice. With a normal diet, SIRT3-deficient animals appear phenotypically normal, in accordance with previous studies (Schwer et al., 2009). However, whereas wild-type mice display lower levels of serum insulin and triglycerides when fed a calorie-restricted diet, SIRT3-deficient mice do not show this response. Based on these results, the authors argue that SIRT3 plays a role in metabolic adaptations to caloric restriction. It remains unclear, however, whether SIRT3 can also mediate the effects of calorie restriction in other tissues or whether it does so specifically in the context of hearing loss.

The authors then investigate the molecular mechanisms involved in this process. Given that caloric restriction reduces age-associated oxidative damage to macromolecules (Sohal and Weindruch, 1996), Someya et al. analyze levels of oxidative damage to DNA in several tissues. They find that a calorie-restricted diet reduces this type of damage in wild-type mice, but not in SIRT3-deficient animals. Importantly, this is the first evidence that a mammalian sirtuin regulates levels of oxidative stress in response to caloric restriction.

But how does SIRT3 regulate oxidative damage during caloric restriction? Given that SIRT3 localizes to the mitochondria, the authors hypothesize that SIRT3 could regulate the antioxidant systems present in this organelle. Using a combination of cellular and biochemical experiments, they discover that SIRT3 regulates the mitochondrial glutathione antioxidant defense system. Glutathione is the main small molecule antioxidant in cells and is generated by glutathione reductase in a reaction dependent on NADPH. The authors show that SIRT3 modulates the

conversion of oxidized glutathione to reduced glutathione in response to caloric restriction. They find that, under these conditions, SIRT3 binds and deacetylates the mitochondrial isocitrate dehydrogenase 2 enzyme (Idh2), the enzyme that generates NADPH, increasing the enzyme's activity. In agreement with these results, Idh2 deacetylation and activity, as well as NADPH levels, increase during caloric restriction in all wild-type tissues tested, whereas SIRT3 deficiency impairs this response. Finally, overexpressing SIRT3 and Idh2 promotes cell viability upon oxidative damage. Together, these data lead the authors to propose a model in which caloric restriction promotes SIRT3 expression, leading to the deacetylation and activation of Idh2, thus providing resistance to oxidative stress and inhibiting the age-related loss of spiral ganglion neurons and hair cells (Figure 1).

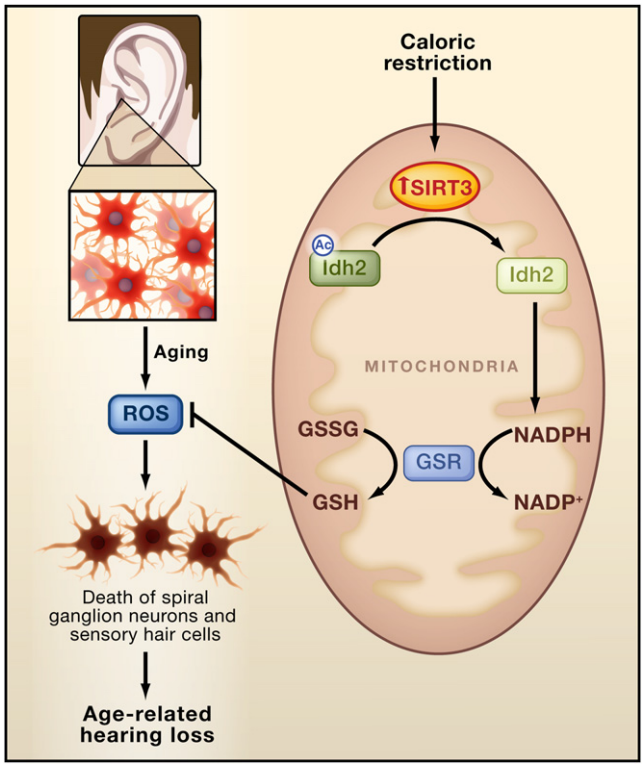

Figure 1. Caloric Restriction, SIRT3, and Age-Related Hearing Loss
During aging (left), oxidative damage (ROS, reactive oxygen species) leads to the loss of spiral ganglion neurons and sensory hair cells in the ear, leading to age-related hearing loss. Caloric restriction (right) prevents the age-associated loss of spiral ganglion neurons and sensory hair cells. Someya et al. (2010) show that caloric restriction leads to an increase in SIRT3 levels in the mitochondria. By promoting the deacetylation of isocitrate dehydrogenase 2 (Idh2), SIRT3 promotes the accumulation of NADPH, hence activating glutathione reductase (GSR), which generates reduced glutathione (GSH), a cellular antioxidant.

Although Someya et al. provide enough data to prove that the effects of caloric restriction on age-related hearing loss are dependent on SIRT3, key questions remain. First, does SIRT3 mediate the effects of caloric restriction in other tissues? And if so, what are its substrates? Multiple mitochondrial proteins are deacetylated upon caloric restriction in a SIRT3-dependent manner (Schwer et al., 2009). It is therefore important to determine whether Idh2 is the main SIRT3 target in preventing oxidative stress or whether other SIRT3 substrates contribute as well. Second, what is the relationship between the effect of SIRT3 on Idh2 and the recently described role for SIRT3 in fatty acid oxidation during nutrient stress (Hirschey et al., 2010)? Are these functions coordinated? If they are not, how is specificity achieved? Third, can we mimic the effects of caloric restriction using SIRT3 activators? If so, such reagents would have significant therapeutic potential. Finally, because other sirtuins also have prominent roles in metabolic regulation (Finkel et al., 2009), can we extend some of these findings to other sirtuins? SIRT1, for example, has been linked to the response of mammals to caloric restriction (Haigis and Guarente, 2006), and it is therefore possible that the activity of this and other sirtuins may be regulated in a coordinated fashion following nutrient starvation.

Regardless of the utopian dream of life span extension, answering some of these questions may provide a step forward for treating age-related pathologies, bringing us closer to a healthier life span. In the words of Francois Jacob, "In a world of unlimited imagination, we are continually inventing a possible world or a piece of a world, and then comparing it with the real world." In the context of sirtuins, it seems we are starting to put some of these pieces together.

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