Scientists ID key protein that links dietary restriction with healthy hearing, aging

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Restricting calories extends life and slows a range of age-related disorders in mice, rats and other organisms. But even after eight decades of research on the subject, scientists are still unclear just how caloric restriction exerts its age-battling influence.

Now, for the first time in mammals, researchers at the University of Florida and colleagues at the University of Wisconsin have sleuthed out the role of a key player in the process, using age-related hearing loss as an example. The protein in question, called Sirt3, could provide a new target for anti-aging drug therapies. The findings are reported in the Nov. 24 issue of the journal *Cell*.

The researchers found that when Sirt3 is absent, caloric restriction loses its anti-aging powers. They uncovered details of how the protein, an enzyme found primarily in mitochondria — the energy-producing centers of cells — wards off cell death by maintaining an environment that combats destructive chemicals.

“Knocking it out seems to be very negative for mitochondrial function and allows the accumulation of oxidative stress and damage to neurons and other cells,” said Christiaan Leeuwenburgh, one of the study’s senior authors who is chief of the biology of aging division in the UF College of Medicine department of aging and geriatric research and a member of the UF Institute on Aging. “That’s an important clue about the role that Sirt3 plays in protecting cells from age-related damage.”

Age-related hearing loss is the most common sensory disorder among the elderly, affecting more than 40 percent of people older than 65 and projected to affect 28 million Americans by 2030, according to the Department of Health and Human Services.

The disorder is marked by the death of sensory hair and nerve cells in the inner ear. While those cells are long-lived, they do not regenerate, so their demise means permanent loss of hearing. But all is not lost, since the environment in which those cells reside can be remodeled over time as damaged organelles such as mitochondria get replaced. Caloric restriction helps to rescue those damaged cells by reducing oxidative damage.

Having previously shown that restricting the diet induces expression of the protein Sirt3 in the inner ear, the researchers now show that Sirt3 aids caloric restriction by combating some of the chemical changes that play a major role in the process of aging.

The enzyme belongs to a class of compounds called sirtuins that are known to have anti-aging effects in lower organisms including yeast and flies. Until now, however, there wasn't clear evidence that the effect extends to mammals.

"This is a major step in terms of understanding aging retardation by dietary restriction — it doesn't work without Sirt3," said Shinichi Someya, first author of the paper and an assistant scientist in genetics and medical genetics at the University of Wisconsin-Madison.

In normal mice, lowering calorie intake to 75 percent of a regular diet reduced hearing loss, but in Sirt3-deficient mice, dietary restriction had no such effect. Further, after caloric restriction, mice lacking Sirt3 lost more cellular structures vital for hearing — sensory hair and nerve cells in the ear — than did normal mice on a similarly restricted diet.

Corresponding with that observation, the researchers found that while caloric restriction reduced oxidative damage to DNA in inner ear cells in normal mice, it did not have that effect in mice that lacked Sirt3.

Closer examination revealed that Sirt3 regulates a mitochondria-based defense mechanism called the glutathione antioxidant system, via which caloric restriction works to help maintain the appropriate chemical balance needed to keep sopping up damaging oxygen-containing chemicals as they appear.

Effects seen in the ear were also observed in brain and liver tissue, suggesting that Sirt3 might have a role well beyond age-related hearing loss, and a potential benefit in cardiovascular and neurological diseases.

“They’ve taken it all the way from the physiological level down to the molecular level,” said S. Michal Jazwinski, a professor of medicine and biochemistry at Tulane University and director of the Tulane Center for Aging, who was not involved in the study. “This may be something that is generally operable in other tissues as well, and may explain the overall caloric restriction effect.”

The new findings identify Sirt3 as a target around which to focus anti-aging therapeutic efforts, including investigating ways to activate its production in the body.

“We’re now finally identifying the major genes involved in the action of caloric restriction, and this provides new opportunities for the development of therapies that may be able to provide the benefits of caloric restriction,” said Tomas Prolla, a professor of genetics and medical genetics at the University of Wisconsin-Madison, who led the research team.

Provided by University of Florida