Researchers find connection between caloric restriction and longevity

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For nearly 70 years scientists have known that caloric restriction prolongs life. In everything from yeast to primates, a significant decrease in calories can extend lifespan by as much as one-third. But getting under the hood of the molecular machinery that drives this longevity has remained elusive.

Now, reporting in the September 21 issue of the journal *Cell*, researchers from Harvard Medical School, in collaboration with scientists from Cornell Medical School and the National Institutes of Health, have discovered two genes in mammalian cells that act as gatekeepers for cellular longevity. When cells experience certain kinds of stress, such as caloric restriction, these genes rev up and help protect cells from diseases of aging.

"We've reason to believe now that these two genes may be potential drug targets for diseases associated with aging," says David Sinclair, associate professor of pathology at Harvard Medical School and senior author on the paper.

The new genes that Sinclair's group have discovered, in collaboration with Anthony Sauve of Cornell Medical School and Rafael de Cabo of NIH, are called SIRT3 and SIRT4. They are members of a larger class of genes called sirtuins. (Another gene belonging to this family, SIRT1, was shown last year to also have a powerful impact on longevity when stimulated by the red-wine molecule resveratrol.)

In this paper, the newly discovered role of SIRT3 and SIRT4 drives home something scientists have suspected for a long time: mitochondria are vital for sustaining the health and longevity of a cell.

Mitochondria, a kind of cellular organ that lives in the cytoplasm, are often considered to be the cell's battery packs. When mitochondria stability starts to wane, energy is drained out of the cell, and its days are numbered. In this paper, Sinclair and his collaborators discovered that SIRT3 and SIRT4 play a vital role in a longevity network that maintains the vitality of mitochondria and keeps cells healthy when they would otherwise die.

When cells undergo caloric restriction, signals sent in through the membrane activate a gene called NAMPT. As levels of NAMPT ramp up, a small molecule called NAD begins to amass in the mitochondria. This, in turn, causes the activity of enzymes created by the SIRT3 and SIRT4 genes--enzymes that live in the mitochondria--to increase as well. As a result, the mitochondria grow stronger, energy-output increases, and the cell's aging process slows down significantly. (Interestingly, this same process is also activated by exercise.)

"We're not sure yet what particular mechanism is activated by these increased levels of NAD, and as a result SIRT3 and SIRT4," says Sinclair, "but we do see that normal cell-suicide programs are noticeably attenuated. This is the first time ever that SIRT3 and SIRT4 have been linked to cell survival."

In fact, the mitochondria appear to be so essential to the cell's life that when all other energy sources inside the cell--including the nucleus--are wiped out, yet the mitochondria are kept intact and functional, the cell remains alive.

"Mitochondria are the guardians of cell survival," says Sinclair. "If we

can keep boosting levels of NAD in the mitochondria, which in turn stimulates buckets more of SIRT3 and SIRT4, then for a period of time the cell really needs nothing else."

Sinclair and his colleagues have coined a phrase for this observation: the Mitochondrial Oasis Hypothesis.

SIRT3 and SIRT4 may now also be potential drug targets for diseases associated with aging. For example, in recent years scientists have become increasingly aware of the importance of mitochondrial function in treating diseases such as cancer, diabetes, and neurodegeneration.

"Theoretically, we can envision a small molecule that can increase levels of NAD, or SIRT3 and SIRT4 directly, in the mitochondria," says Sinclair. "Such a molecule could be used for many age-related diseases."

According to Suave of Cornell, "This study also highlights how advanced technological methods can help resolve fundamental biological questions in ways that were hard to achieve as recently as a few years ago."

Source: Harvard Medical School