Genetic switch could be key to increased health and lifespan

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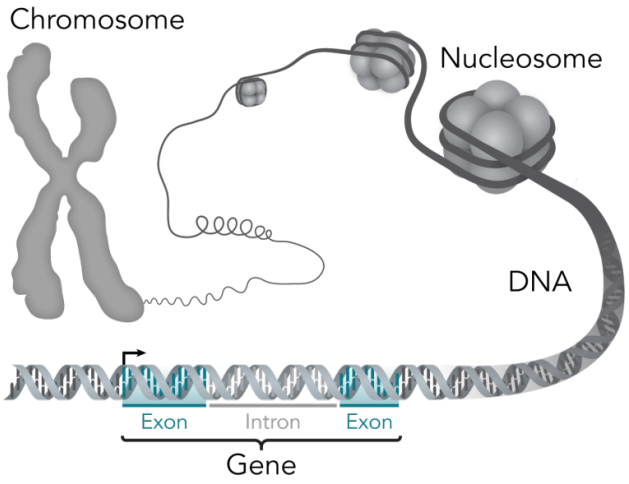

This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas Splettstoesser/Wikipedia/CC BY-SA 4.0

Newly discovered genetic switches that increase lifespan and boost fitness in worms are also linked to increased lifespan in mammals, offering hope that drugs to flip these switches could improve human metabolic function and increase longevity.

These so-called epigenetic switches, discovered by scientists at the University of California, Berkeley, and the École Polytechnique Fédérale de Lausanne in Switzerland, are enzymes that are ramped up after mild stress during early development and continue to affect the expression of genes throughout the animal's life.

When the researchers looked at strains of inbred mice that have radically different lifespans, those with the longest lifespans had significantly higher expression of these enzymes than did the short-lived mice.

"Two of the enzymes we discovered are highly, highly correlated with lifespan; it is the biggest genetic correlation that has ever been found for lifespan in mice, and they're both naturally occurring variants," said Andrew Dillin, a UC Berkeley professor of molecular and cell biology. "Based on what we see in worms, boosting these enzymes could reprogram your metabolism to create better health, with a possible side effect of altering lifespan."

These are the first epigenetic modifiers known to affect metabolic function and longevity, though others are known to affect either metabolism or lifespan.

The discoveries will be reported in two papers to appear in the May 19 issue of the journal *Cell*. Both are now available online. Dillin and Johan Auwerx at the EPFL led an international team that is publishing one paper, while Dillin and his UC Berkeley colleagues, including Barbara Meyer, a professor of molecular and cell biology, authored the second.

Starvation leads to longer life spans

For decades, researchers have found correlations between nutrient availability during early development and adult health and metabolism. Brief changes in the energy available to the cell - caused by restricting diet, for example - seem to reshape animal physiology for years to come, even affecting lifespan.

"What if the amount of nutrients an infant consumed determined whether he became diabetic or obese as an adult?" said Dillin, who is also co-director of the Glenn Center for Aging Research, a

joint UC Berkeley/UC San Francisco program. "What if the metabolic state of a child affected how long she lived, or whether she would develop a neurodegenerative disease?"

These observations led to the idea that reducing cellular energy production could slow the aging process and make organisms live longer.

Puzzlingly, these energy restrictions had to occur during a specific window of development in order to affect the aging process, suggesting the existence of a critical metabolic switch that could remodel cellular functions throughout the organism´s entire lifespan. The mechanisms of how these changes were sensed and perpetuated, however, remained elusive, though researchers have focused their search on the power factory of the cell, the mitochondria.

Malfunctioning mitochondria have been reported as a cause or a consequence of nearly every single age-onset human disease, Dillin said, including Alzheimer's and Parkinson's disease, heart disease, type 2 diabetes and cancer. When mitochondrial function is shut down during a specific period of development in model organisms, the animals live longer. These transient metabolic changes appear capable of restructuring the way our cells read our DNA, shutting down the use of some genes, while amplifying the expression of others - ultimately affecting health into adulthood.

In 2002, Dillin discovered that stressing the mitochondria during development nearly doubled the worm's lifespan. In the new studies, the researchers have begun to sketch out how this works.

They found that mitochondrial stress activates enzymes in the brain that affect DNA folding, exposing a segment of DNA that contains the 1,500 genes involved in the work of the mitochondria. A second set of enzymes then tags these genes, affecting their activation for much or all of the lifetime of the animal and causing permanent changes in how the mitochondria generates energy.

The brain's hunger switch

The first set of enzymes - methylases, in particular LIN-65 - add methyl groups to the DNA, which can silence promoters and thus suppress gene expression. By also opening up the mitochondrial genes, these methylases set the stage for the second set of enzymes - demethylases, in this case jmjd-1.2 and jmjd-3.1 - to ramp up transcription of the mitochondrial genes. When the researchers artificially increased production of the demethylases in worms, all lived longer, a result identical to what is observed after mitochondrial stress.

"By changing the epigenetic state, these enzymes are able to switch genes on and off," Dillin said.

This happens only in the brain of the worm, however, in areas that sense hunger or satiety.

"These genes are expressed in neurons that are sensing the nutritional status of the animal, and these signals emanate out to the periphery to change peripheral metabolism," he said.

When they profiled enzymes in short- and long-lived mice, they found up-regulation of these genes in the brains of long-lived mice, but not in other tissues or in the brains of short-lived mice.

"These genes are expressed in the hypothalamus, exactly where, when you eat, the signals are generated that tell you that you are full. And when you are hungry, signals in that region tell you to go and eat," he said. "These genes are all involved in peripheral feedback. "

Among the mitochondrial genes activated by these enzymes are those involved in the body's response to proteins that unfold, which is a sign of stress. Increased activity of the proteins that refold other proteins is another hallmark of longer life.

These observations suggest that the reversal of aging by epigenetic enzymes could also take place in humans.

"It seems that, while extreme metabolic stress can lead to problems later in life, mild stress early in development says to the body, 'Whoa, things are a little bit off-kilter here, let's try to repair this and make it better.' These epigenetic switches keep this

up for the rest of the animal's life," Dillin said.

More information: Ye Tian et al, Mitochondrial Stress Induces Chromatin Reorganization to Promote Longevity and UPRmt, *Cell* (2016). DOI: 10.1016/j.cell.2016.04.011