Turning off the 'aging genes'

January 2 2014

Restricting calorie consumption is one of the few proven ways to combat aging. Though the underlying mechanism is unknown, calorie restriction has been shown to prolong lifespan in yeast, worms, flies, monkeys, and, in some studies, humans.

Now Keren Yizhak, a doctoral student in Prof. Eytan Ruppin's laboratory at Tel Aviv University's Blavatnik School of Computer Science, and her colleagues have developed a computer algorithm that predicts which genes can be "turned off" to create the same anti-aging effect as calorie restriction. The findings, reported in *Nature Communications*, could lead to the development of new drugs to treat aging. Researchers from Bar-Ilan University collaborated on the research.

"Most algorithms try to find drug targets that kill cells to treat cancer or

bacterial infections," says Yizhak. "Our algorithm is the first in our field to look for drug targets not to kill cells, but to transform them from a diseased state into a healthy one."

A digital laboratory

Prof. Ruppin's lab is a leader in the growing field of genome-scale metabolic modeling or GSMMs. Using mathematical equations and computers, GSMMs describe the metabolism, or life-sustaining, processes of living cells. Once built, the individual models serve as digital laboratories, allowing formerly labor-intensive tests to be conducted with the click of a mouse. Yizhak's algorithm, which she calls a "metabolic transformation algorithm," or MTA, can take information about any two metabolic states and predict the environmental or genetic changes required to go from one state to the other.

"Gene expression" is the measurement of the expression level of individual genes in a cell, and genes can be "turned off" in various ways to prevent them from being expressed in the cell. In the study, Yizhak applied MTA to the genetics of aging. After using her custom-designed MTA to confirm previous laboratory findings, she used it to predict genes that can be turned off to make the gene expression of old yeast look like that of young yeast. Yeast is the most widely used genetic model because much of its DNA is preserved in humans.

Some of the genes that the MTA identified were already known to extend the lifespan of yeast when turned off. Of the other genes she found, Yizhak sent seven to be tested at a Bar-Ilan University laboratory. Researchers there found that turning off two of the genes, GRE3 and ADH2, in actual, non-digital yeast significantly extends the yeast's lifespan.

"You would expect about three percent of yeast's genes to be lifespan-

extending," said Yizhak. "So achieving a 10-fold increase over this expected frequency, as we did, is very encouraging."

Hope for humans

Since MTA provides a systemic view of cell metabolism, it can also shed light on how the genes it identifies contribute to changes in genetic expression. In the case of GRE3 and ADH2, MTA showed that turning off the genes increased oxidative stress levels in yeast, thus possibly inducing a mild stress similar to that produced by calorie restriction.

As a final test, Yizhak applied MTA to human metabolic information. MTA was able to identify a set of genes that can transform 40-to-70 percent of the differences between the old and young information from four different studies. While currently there is no way to verify the results in humans, many of these genes are known to extend lifespan in yeast, worms, and mice.

Next, Yizhak will study whether turning off the genes predicted by MTA prolongs the lifespan of genetically engineered mice. One day, drugs could be developed to target genes in humans, potentially allowing us to live longer. MTA could also be applied to finding drug targets for disorders where metabolism plays a role, including obesity, diabetes, neurodegenerative disorders, and cancer.

More information: *Nature Communications* 4, Article number: 2632
DOI: 10.1038/ncomms3632

Provided by Tel Aviv University

Citation: Turning off the 'aging genes' (2014, January 2) retrieved 26 April 2024 from https://phys.org/news/2014-01-aging-genes.html

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