Slowing the aging process—only with antibiotics

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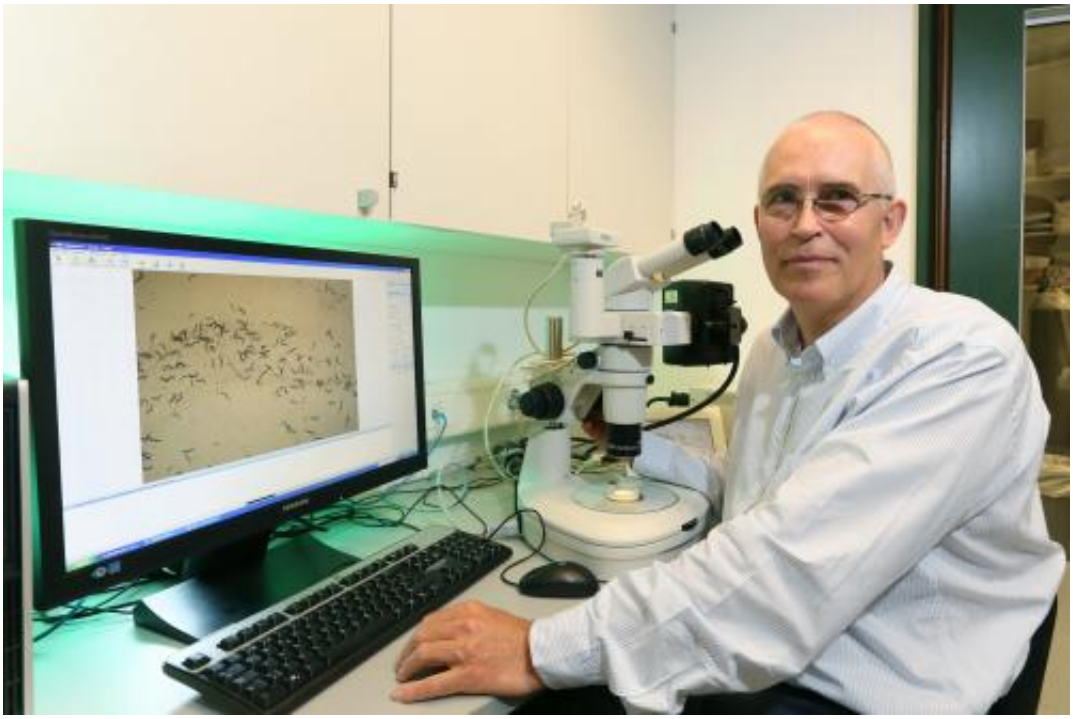

Johan Auwerx, Nestlé Chair in metabolism at EPFL, head of the Laboratory of Integrative Systems Physiology (LISP), identified a group of genes whose expression have an essential impact on longevity. Credit: EPFL / Alain Herzog

Swiss scientists reveal the mechanism responsible for aging hidden deep within mitochondria—and dramatically slow it down in worms by administering antibiotics to the young.

Why is it that within a homogeneous population of the same species,

some individuals live three times as long as others? This question has stumped scientists for centuries.

Now, EPFL researchers led by Johan Auwerx report in the journal *Nature* how a mechanism in mice plays a determining role in longevity. And they go a step further: by disrupting this mechanism using simple antibiotics in a population of nematodes, or roundworms, they can multiply lifespan by a factor of 1.6.

Mitochondia: biological timekeepers

The process identified by EPFL scientists takes place within organelles called mitochondria, known as the cellular powerhouses because they transform nutrients into proteins including adenosine triphosphate (ATP), used by muscles as energy.

But that's not all they do. Several studies have shown that mitochondria are also involved in aging. The new EPFL research, done in collaboration with partners in the Netherlands and the US, pinpoints the exact genes involved and measures the consequences to longevity when the amount of protein they encode for is varied: less protein, longer life.

Natural variations in mice

Laboratory mice in the BXD reference population typically live from 365 to 900 days. This population, which reflects genetic variations that occur naturally within a species, is used by many researchers in an approach known as "real-world genetics." The benefit of working with this population in particular is that their genome is almost completely decoded.

The team led by professor Auwerx, head of EPFL's Laboratory of

Integrative and Systemic Physiology, analyzed mice genomes as a function of longevity and found a group of three genes situated on chromosome number two that, up to this point, had not been suspected of playing any role in aging. But the numbers didn't lie: a 50 percent reduction in the expression of these genes—and therefore a reduction in the proteins they code for—increased mouse life span by about 250 days.

Extending life in worms

Next, the team reproduced the protein variations in a species of nematode, *Caenorhabidtis elegans*. "By reducing the production of these proteins during the worms' growth phase, we significantly increased their longevity," says Auwerx.

The average life span of a worm manipulated in this way went from 19 to more than 30 days, an increase of 60 percent. The scientists then conducted tests to isolate the common property and determined that the presence of mitochondrial ribosomal proteins (MRPs) is inversely proportional to longevity.

Life-prolonging stress

The researchers concluded that a lack of MRP at certain key moments in development created a specific stress reaction known as an "unfolded protein response" within the mitochondria. "The strength of this response was found to be directly proportional to the life span," says Auwerx. "However, we noted that it was more pronounced if the protein imbalance—the reduction in MRP— occurred at a young age. A similar stimulation in an adult did not affect the worms' longevity."

What's more, the effect can be induced without genetically manipulating the worms. "Exposure to certain readily available drugs inhibits

ribosomal function and thus causes the desired reaction," says Auwerx. In other words, mitochondria are sensitive to certain antibiotics, and the drugs can be used to prolong life.

Weary youngsters, vigorous old folks

Worms given antibiotics don't just live to ripe old age. At maturity, which is 13 days, they also moved twice as much as the others, according to Laurent Mouchiroud, co-author of the study. "Around 20 days of age, the difference was even more pronounced because the 'control' individuals were often already in bad shape," he adds.

Using a software program modified by colleagues in EPFL's School of Computer and Communications Sciences, Mouchiroud was able to follow, measure and qualify the movements of many worms during their entire life, and he observed that those who had undergone drug treatment had superior endurance and energy. "In addition, their muscles were in better shape," he reports.

However, individuals who were given the antibiotics early in life—for example in the larval stage—also presented several less favorable characteristics. Their development was slightly slower, they laid fewer eggs and they had less energy at about three days old, the outset of adult development. "This reminded us of the vaguely flu-like state one gets right after the administration of a vaccine," says Monchiroud. "But the stress reaction in the mitochondria, and thus the potential for increased longevity, remained after the treatment phase."

All indications are that the observed and proven mechanisms in worms should be similar to those in mice, and therefore possibly in other mammals. Further studies are necessary, of course, to confirm that aging and its deleterious effects could be slowed down in mammals using antibiotics at precise moments in development.

"This research gives us hope not only for increasing longevity, but also for lengthening the period of adult vitality, and doing this with simple drugs such as antibiotics," concludes Auwerx.

More information: Paper: dx.doi.org/10.1038/nature12188

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