



Research in Context: Can We Slow Aging?

Research explores the biology of aging, including how to measure its speed and progression and ways it might be slowed down or even reversed.

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With advancing age comes an increased risk of disease and disability. As people live longer, they are more likely to develop at least one age-related disease. And as the global population gets older, the global burden of these diseases is expected to grow. Instead of treating each individual disease as it arises, a more effective way to reduce this burden would be to attack them at their common root: the aging process itself.

Scientists today understand aging as the tendency that all things have to degrade over time. Dr. Tony Wyss-Coray, who studies brain aging and neurodegeneration at Stanford University, likens it to what happens to a car. “You get it off the lot and it’s all shiny, and everything works perfectly. As you keep driving it over the years, all the parts look older. It may still run fine, but the exposure to the elements and usage leads to a growing level of wear and tear and then ultimately dysfunction.”

Similarly, aging in people results from the gradual accumulation of defects and damage to the molecules and cells that make up our bodies. Unlike a car, our bodies have built-in mechanisms for repairing this damage. But even these repair mechanisms wear out over time. Eventually, enough damage accumulates to affect the function of whole organs and systems.

NIH-funded researchers have been working to better understand aging at the molecular level. They’re studying ways to measure differences in how people age before health problems appear. They’re also exploring possible ways to slow, or even reverse, aging at the molecular level. This could lead to better approaches to prevent or treat age-related disease and disability.

Measuring aging

Before you can tell if a treatment could slow or even reverse aging, you need to know how fast someone is aging in the first place. It’s no secret that people age at different rates. Some people remain healthy and disease-free well into their ninth or even tenth decade of life. Others develop age-related diseases, such as cancer, heart disease, and dementia, much earlier. The concept of “biological age” is often used to describe these differences. Biological age reflects the molecular

damage that accumulates over the years and eventually leads to disease and disability.

Differences in biological age can develop years before age-related diseases appear. So a treatment to slow aging would also need to start well before such diseases appear. Then, to find out if a treatment worked or not, you'd have to track people for the rest of their lives. That's why researchers have been working to develop "aging clocks" to measure a person's biological age.

One approach is to measure various biomarkers and compare them to what's typical for a given chronological age. Dr. Daniel Belsky, who studies aging at the Columbia Mailman School of Public Health, explains, "We use the general population as a reference, and we say, 'the average 50-year-old looks like this, the average 60-year-old looks like this, the average 70-year-old looks like this.' We take your biomarker levels and line them up against that population average, and we say, 'Aha, you look about like a 55-year-old, so we're going to call you biologically 55.' If you happen to be 65 years old, that's great news. If you happen to be 45, it's not great news."

Belsky has taken this a step further. Instead of just an aging clock, which shows how much someone has aged, Belsky's team, in collaboration with Dr. Terrie Moffitt's team at Duke University and the Dunedin Longitudinal Study, developed an aging "speedometer." It shows how fast or slow someone is aging.

The researchers focused on chemical modifications to DNA, called DNA methylation, that change with age. To develop the measure, they used data from the Dunedin Study, a long-term health study of more than 1,000 people born in New Zealand in 1972-1973. As part of the study, participants received comprehensive health evaluations at four time points from ages 26 to 45. These gathered DNA methylation data from blood samples and 19 biomarkers that track the function of various organ systems. Using machine-learning tools, the team developed an algorithm to identify DNA methylation patterns at age 45 that correlate with changes in the 19 biomarkers over a 20-year period. They named this algorithm DunedinPACE (Dunedin Pace of Aging Calculated from the Epigenome).

Belsky and his colleagues then applied DunedinPACE to data from other long-term studies. People in these studies with a faster rate of aging, as measured by DunedinPACE, had a greater risk of poor health, developing chronic disease, or dying earlier.

Belsky hopes that DunedinPACE could be used to test age-slowng interventions. It could also help to identify people who are aging faster than normal, and so at greater risk of age-related disease. "Say I'm 45 this year and I'm going to age into eligibility for certain cancer screenings," he explains. "If I was aging biologically more rapidly, my doctor might think, 'Oh, you know what, we should start some of these screenings a year or two earlier.' Or if I'm aging slowly, they might say, 'you know, you could decide to wait a year or two.'"

It turns out that different organs can age at different rates, too, even in the same person. So, for example, someone might have a heart that's aged more than the rest of their body. Wyss-Coray has shown that it's possible to measure the aging of individual organs based on levels of certain proteins in the blood. Accelerated aging in a specific organ increases the risk of diseases affecting

that organ. So, knowing the aging rates of individual organs could help to further focus care on those organs most likely to cause problems in the future.

Rejuvenating old brains

Among the most serious health effects of aging are in the brain. As we age, the ability of neurons to strengthen connections, called synaptic plasticity, decreases. Synaptic plasticity, particularly in a region of the brain called the hippocampus, is required for learning and memory. Thus, the loss of plasticity with age can lead to cognitive impairment and increased susceptibility to neurodegenerative diseases. Preserving or restoring this ability might keep people cognitively healthy and able to live independently for longer.

In 2014, Wyss-Coray and his colleagues showed that blood from young mice could have beneficial effects on the brains of aged mice. When the blood of a young mouse was introduced into an old mouse, it altered how genes related to synaptic plasticity were activated, or expressed, in the aged mouse. It also increased measures of plasticity in the hippocampus of the aged mouse. When the researchers injected aged mice with blood plasma from young mice, it improved learning and memory. These results suggested that something in the young mice's blood could reverse the age-related loss of plasticity.

About the youngest blood you can get is from the umbilical cord at birth. Injecting aged mice with plasma from human umbilical cord blood had similar effects on gene expression, plasticity, and cognitive function as plasma from young mice. So, whatever anti-aging factor was in young mouse plasma could also be found in human cord plasma.

To find out what this factor might be, the team compared proteins in cord plasma and plasma from young and aged mice and humans. They zeroed in on a protein called tissue inhibitor of metalloproteinases 2 (TIMP2). TIMP2 could also be found in the mouse hippocampus, where its levels declined with age. Injecting aged mice with TIMP2 increased its level in the brain, promoted plasticity in the hippocampus, and improved learning and memory. When cord blood was depleted of TIMP2, it had no effect on learning and memory in aged mice. This showed that TIMP2 was responsible for these effects.

The findings suggest that plasma from young donors, or components of their plasma, might be used to treat neurodegeneration. Wyss-Coray founded a company, Alkahest Inc., to perform clinical trials of this approach. But it may be some time before plasma-based treatments are ready for widespread use. More generally, Wyss-Coray's findings support the notion that at least some of the consequences of aging are reversible.

Restricting calorie

Age-reversing therapies like these are still some way in the future. Are there measures people can take now to at least slow the aging process?

"Absolutely," Belsky says, "and none of them are very exciting." The things people already do to

stay healthy in general are also the best ways to stave off the effects of aging. “Physical activity is the closest thing to a fountain of youth that we know of,” he explains. Healthy eating can also play a major role in staving off the effects of aging.

Still, there are hints of lifestyle interventions that may have potential to lengthen life and delay aging. One that’s been particularly well-studied is calorie restriction (CR). This is where you reduce the total number of calories you consume, but still get enough of the essential nutrients. From yeast to rodents, studies have found that CR can increase longevity and delay age-related diseases.

To find out whether CR might have benefits in humans, too, NIH funded the Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) study. More than 200 healthy, middle-aged volunteers were randomly assigned to two groups. Participants in one group were challenged to reduce their daily caloric intake by 25% for two years and given dietary and behavioral strategies for doing so. Those in the other group continued to eat their normal diets.

Participants in the CR group managed to achieve an average 12.5% calorie reduction. For a 2,000 calorie-per-day diet, that amounts to 250 fewer calories per day, about the number of calories in a bagel. Participants lost an average of 10% of their body weight, mostly from fat.

Researchers led by Belsky examined the pace of biological aging in CALERIE participants. Those in the CR group had a much slower pace of aging as measured by clinical blood biomarkers. They also had a small but significant decrease in DunedinPACE, while participants in the other group did not.

One interesting result was that CR led to a small but significant decline in muscle tissue. But there was no significant decline in muscle strength. This suggests that CR may have improved the quality of muscle in the body.

Researchers wanted to explore this result further and find out how CR improved muscle health. The team was led by Luigi Ferrucci, the scientific director of NIH’s National Institute on Aging (NIA), and also included Belsky. They analyzed thigh muscle biopsies taken from a subset of CALERIE participants at the start of the study and at one-year intervals.

The team identified more than 1,000 genes whose expression differed between the CR and control groups. Many of the affected genes had already been found to be affected by CR in animal models. Gene expression increased in biological pathways related to muscle formation and repair, circadian clock regulation, and mechanisms tied to aging. Meanwhile, expression decreased in pathways related to inflammation. Several of these pathway changes appeared to mediate the effect of CR on muscle strength.

Notably, CR also had an effect on RNA splicing. Genes must be transcribed into messenger RNA (mRNA) before they can be translated into protein. This mRNA undergoes splicing to reach its final form. A single gene can thus produce more than one protein if its mRNA gets spliced in different ways. CR led to changes in the splicing variants produced from many genes, including those

involved in muscle physiology and aging.

Over the long term, CR might be able to prevent age-related declines in muscle function. Ferrucci is optimistic that even a small amount of CR could go a long way toward preserving people's health as they age, although further study is needed.

But Ferrucci echoes Belsky's view that there are many practical measures that we already know can slow aging. "Being physically active is the best gift that you can give to yourself," he says.

Other measures he recommends include not smoking, maintaining a healthy weight, getting good sleep, getting all recommended vaccines, getting preventive cancer screenings, and treating hypertension and high cholesterol. "People have demonstrated that if you do these things, which are all feasible, you can increase your life expectancy by 10 years. We don't need a magic pill," he adds. "The magic pill is already here."

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