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# Why Our Biological Clock Ticks: Research Reconciles Major Theories of Aging

Two prominent explanations for aging are not so different after all; results call current anti-aging strategies into question



Two major theories of aging both involve DNA, but in very different ways. Researchers at UC San Diego have revealed that these theories may not be so different after all. Photo credit: UC San Diego Health Sciences/Adobe Firefly

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Researchers at University of California San Diego School of Medicine have published results that shed new light on an old question: what causes aging at the molecular level? Their findings, published in

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Nature Aging, describe a never-before-seen link between the two most accepted explanations: random genetic mutations and predictable epigenetic modifications. The latter, also known as the epigenetic clock theory, has been widely used by scientists as a consistent, quantitative measure of biological aging.

However, the new research suggests that the process may not be so simple.

“Major research institutions and companies are betting on turning back the epigenetic clock as a strategy to reverse the effects of aging, but our research suggests that this may only be treating a symptom of aging, not the underlying cause,” said co-corresponding author Trey Ideker, Ph.D., a professor at UC San Diego School of Medicine and UC San Diego Jacobs School of Engineering. “If mutations are in fact responsible for the observed epigenetic changes, this fact could fundamentally change the way we approach anti-aging efforts in the future.”

There are two prevailing theories about the relationship between aging and DNA. The somatic mutation theory suggests that aging is caused by the accumulation of mutations, permanent changes in our DNA sequence that occur randomly. The epigenetic clock theory suggests that aging occurs due to the accumulation of epigenetic modifications, minor changes to the chemical structure of DNA that do not alter the underlying sequence, but instead change which genes are on or off. Unlike mutations, epigenetic modifications can also be reversed in some cases.

Because epigenetic modifications only occur at specific sites on our genome rather than at random locations, they are easier to quantify and have become a go-to way for scientists

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Using patient data from several banks of genomics data, researchers at UC San Diego were able to make similar predictions of aging using either mutations or epigenetic modifications. Their results reveal a common link between two separate but equally prominent theories of aging. Photo by Kyle Dykes/UC San Diego Health Sciences

to determine the “biological age” of cells. However, scientists have long wondered about the source of these epigenetic changes.

To answer this fundamental question, researchers analyzed data from 9,331 patients catalogued in the Cancer Genome Atlas and the Pan-Cancer Analysis of Whole Genomes. By comparing genetic mutations to epigenetic modifications, they found that mutations were predictably correlated with changes in DNA methylation, one type of epigenetic modification. They found that a single mutation could cause a cascade of epigenetic changes across the genome, not just where the mutation occurred. Using this relationship, the researchers were able to make similar predictions of age using either mutations or epigenetic changes.

“Epigenetic clocks have been around for years, but we’re only now beginning to answer the question of why epigenetic clocks tick in the first place,” said first author Zane Koch, a Ph.D. candidate in bioinformatics at UC San Diego. “Our study demonstrates for the first time that epigenetic changes are intricately and predictably tied to random genetic mutations.”

The study's authors note that further research is needed to fully understand the relationship between somatic mutations and epigenetic changes in aging. However, the study's findings provide a major breakthrough in our understanding of the aging process and have important implications for the development of new therapies aimed at preventing or reversing aging.

"If somatic mutations are the fundamental driver of aging and epigenetic changes simply track this process, it's going to be a

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Trey Ideker

lot harder to reverse aging than we previously thought," added co-corresponding author Steven Cummings, M.D., executive director of the San Francisco Coordinating Center at UC San Francisco and senior research scientist at Sutter Health's California Pacific Medical Center Research Institute. "This shifts our focus from viewing aging as a programmed process to one that's largely influenced by random, cumulative changes over time."



First author Zane Koch is a PhD candidate in bioinformatics at UC San Diego.

Read the [full study](#).

In addition to Ideker, Cummings and Koch, the study was co-authored by Adam Li at UC San Diego and Daniel S. Evans at California Pacific Medical Center Research Institute and UC San Francisco.

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*Disclosures: Trey Ideker is a cofounder of Serinus and Data4Cure, is on their Scientific Advisory Boards, and has equity interest in both companies. Scientific Advisory Board of Ideaya BioSciences and has an equity interest.*

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