Accelerating the human aging clock by mutating an epigenetic gene

Alison Liu[1]

[1]Genetics & Genomics Next Editors

April 28, 2020

The biological age of human tissues and cells may be younger or older than the expected chronological age. Many genetic and environmental factors can contribute to this difference. Recently, scientists have developed various clocks to measure the biological age in humans. Among them, the Horvath epigenetic aging clock, a multi-tissue predictor of age, is the most widely used one. It can cover both pre- and postnatal lifespans and has proven to be accurate. However, it remains unknown how its clock ticking rate is controlled.

It was believed that the epigenetic aging clocks tick due to the erosion of a hypothetical "epigenetic maintenance system", in which the epigentic genes set the ticking rate.

Epigenetic genes encode proteins that modify DNA or histone proteins chemically, which can in turn change the binding or access of regulatory proteins (i. e. transcription factors) to the DNA regions that control gene expression (i. e. promoters and enhancers), thus affecting gene expression. Unlike genetic mutations, epigenetic modifications are reversible, do not change DNA or protein sequences, and can occur in response to environmental and developmental cues.

The Horvath clock is made of mathematical models, which are based on a small set of cytosine methylation (mC) changes at the CpG ("p" represents a phosphodiester bond between cytosine and guanine) sites in the human genome. About one half of the CpG sites increases in methylation while the other half decreases during aging. The clock is set near "zero" for newborn cells, such as embryonic and pluripotent stem cells, and the "time" increases due to the methylation changes. For each tissue, the clock has a unique aging rate. The DNA methylation data can be obtained applying blood samples to the Illumina Human-Methylation450 array (450K array), and the "time" value can be calculated using an online calculator of computational algorithms (`https://dnamage.genetics.ucla.edu/home`).

A study by (Martin-Herranz et al., 2019) has identified NSD1, the first gene in the "epigenetic maintenance system" to have accelerated the Horvath aging clock. The team screened for the epigenetic genes that could accelerate the ticking rate of the Horvath clock in the patients who suffered from developmental diseases due to the mutations of these genes. They measured the clock aging rate in blood samples and found that only the Sotos syndrome patients had significantly accelerated clock aging rate. Sotos syndrome is caused by NSD1 mutations and has a range of aging-like developmental symptoms such as "prenatal and postnatal overgrowth, facial gestalt, advanced bone age, developmental delay, higher cancer predisposition, and, in some cases, heart defects".

NSD1 encodes a Histone H3 lysine 36 (H3k36) methyltransferase, an epigenetic regulatory enzyme that can add a mono- or di-methyl group to the 36th amino acid, lysine (K), of the histone H3 protein. Histone H3

is one of eight histone proteins packing the genomic DNA to form nucleosomes.

The researchers then conducted genome-wide analyses, confirming that the NSD1 mutations in Sotos syndrome affected many CpG methylation sites, some of which were also affected by aging. The measurement strategy was more accurate than the Horvath clock because the calibrations used a large number of control samples and a microarray-based method.

Previous studies support that NSD1 can change the ticking rate. For example, NSD1 can affect DNA methylation indirectly by interacting with DNA methylation machinery. Several NSD1 interacting proteins in humans or their homologs in other species have been shown to affect the aging rate.

This study has established the pivotal role of the H3k36 methyltransferase gene, NSD1, in the epigenetic maintenance system to determine the ticking rate of the epigenetic aging clock. It showed that the clock is at least partially controlled genetically, if not entirely. Interestingly, the clock may have a functional role in the aging process. This study has provided an excellent model for investigating many questions related to the human aging rate.

The aging clock, due to its reversible epigenetic nature, may be reset with proper intervention, including keeping a healthy life style such as eating a low-calorie diet, exercising , and staying happy and positive.

Author ORCiD

Alison Liu https://orcid.org/0000-0003-0171-6441

References

Screening for genes that accelerate the epigenetic aging clock in humans reveals a role for the H3K36 methyltransferase NSD1. (2019). *Genome Biology*, *20*(1). https://doi.org/10.1186/s13059-019-1753-9