Our cells are less likely to express longer genes as we age, researchers say

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Aging may be less about specific "aging genes" and more about how long a gene is. Many of the changes associated with aging could be occurring due to decreased expression of long genes, say researchers in an opinion piece published March 21 in the journal *Trends in Genetics*.

A decline in the expression of long genes with age has been observed in

a wide range of animals, from worms to humans, in various human cell and tissue types, and also in individuals with neurodegenerative disease. Mouse experiments show that the phenomenon can be mitigated via known anti-aging factors, including dietary restriction.

"If you ask me, this is the main cause of systemic aging in the whole body," says co-author and molecular biologist Jan Hoeijmakers of the Erasmus University Medical Center, Rotterdam; the University of Cologne; and Oncode Institute/Princess Maxima Institute, Utrecht.

The authors span four research groups from Spain, the Netherlands, Germany, and the United States, with each group arriving at the same conclusions using different methods.

Aging is associated with changes at the molecular, cellular, and organ level—from altered protein production to sub-optimal cell metabolism to compromised tissue architecture. These changes are thought to originate from DNA damage resulting from cumulative exposure to harmful agents such as UV radiation or reactive oxygen species generated by our own metabolism.

While a lot of research in aging has focused on specific genes that might accelerate or slow aging, investigations of exactly which genes are more susceptible to aging have revealed no clear pattern in terms of gene function. Instead, susceptibility seems to be linked to the genes' lengths.

"For a long time, the aging field has been focused on genes associated with aging, but our explanation is that it is much more random—it's a physical phenomenon related to the length of the genes and not to the specific genes involved or the function of those genes," says co-author Ander Izeta of the Biogipuzkoa Health Research Institute and Donostia University Hospital, Spain.

It essentially comes down to chance; long genes simply have more potential sites that could be damaged. The researchers compare it to a road trip—the longer the trip, the more likely that something will go wrong. And because some cell types tend to express long genes more than others, these cells are more likely to accumulate DNA damage as they age.

Cells that don't (or very rarely) divide also seem to be more susceptible compared to rapidly replicating cells because long-lived cells have more time to accumulate DNA damage and must rely on DNA repair mechanisms to fix them, whereas rapidly dividing cells tend to be short-lived.

Because neural cells are known to express particularly long genes and are also slow or non-dividing, they are especially susceptible to the phenomenon, and the researchers highlight the link between aging and neurodegeneration.

Many of the genes involved in preventing protein aggregation in Alzheimer's disease are exceptionally long, and pediatric cancer patients, who are cured by DNA-damaging chemotherapy, later suffer from premature aging and neurodegeneration.

The authors speculate that damage to long genes could explain most of the features of aging because it is associated with known aging accelerants and because it can be mitigated with known anti-aging therapies, such as dietary restriction (which has been shown to limit DNA damage).

"Many different things that are known to affect aging seem to lead to this length-dependent regulation, for example, different types of irradiation, smoking, alcohol, diet, and oxidative stress," says co-author Thomas Stoeger of Northwestern University.

However, although the association between the decline in long-gene expression and aging is strong, causative evidence remains to be demonstrated. "Of course, you never know which came first, the egg or the chicken, but we can see a strong relationship between this phenomenon and many of the well-known hallmarks of aging," says Izeta.

In future studies, the researchers plan to further investigate the phenomenon's mechanism and evolutionary implications and to explore its relationship with neurodegeneration.

More information: Time is ticking faster for long genes in aging, *Trends in Genetics* (2024). DOI: 10.1016/j.tig.2024.01.009

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