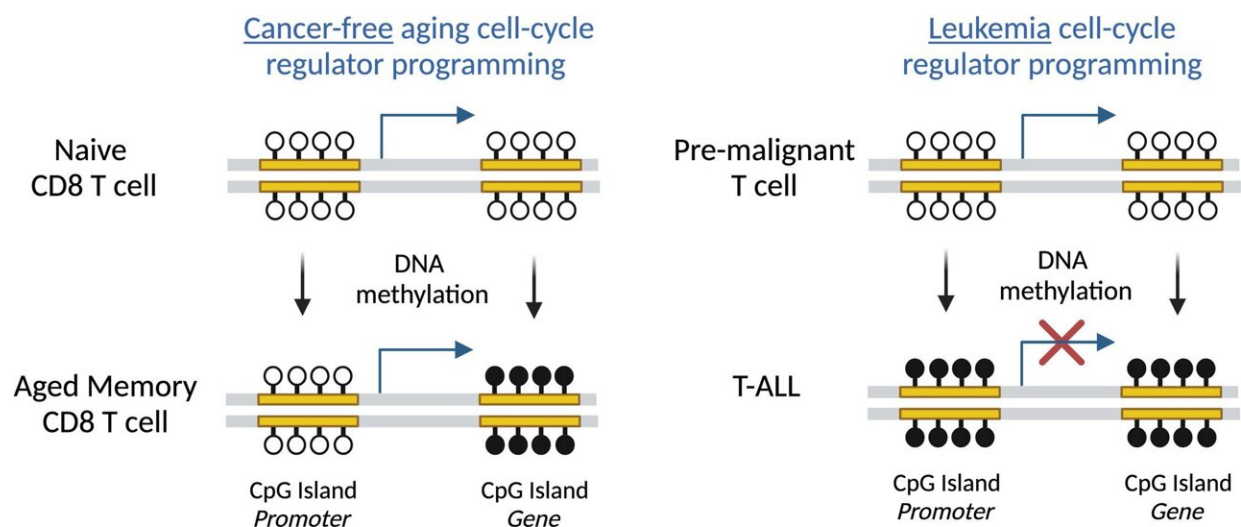


Age is just a number: Immune cell 'epigenetic clock' ticks independently of organism lifespan

June 12 2024



Cartoon summary of experiential age-associated DNA methylation programs that delineate longevity versus malignancy among T cells. Credit: *Nature Aging* (2024). DOI: 10.1038/s43587-024-00649-5

While most cell types experience a functional decline after years of proliferation and replication, T cells can proliferate seemingly indefinitely and without detriment.

Scientists at St. Jude Children's Research Hospital and the University of Minnesota investigated the unique 'epigenetic clock' of T cell aging,

demonstrating that T cells can outlive an organism through at least four lifetimes. In addition, the researchers showed that healthy T cell age was uncoupled from the organism's chronologic age.

Furthermore, they determined that malignant T cells from [pediatric patients](#) with T cell [acute lymphoblastic leukemia](#) (T-ALL) appeared to have aged up to 200 years. [The findings were published](#) in *Nature Aging*.

As researchers explore the process of cellular aging through repeat replicative cycles of growth, some peculiar patterns have emerged regarding T cells.

"The immune system by nature must mount a rapid proliferative response to a pathogen or a tumor," said co-corresponding author Ben Youngblood, Ph.D., St. Jude Department of Immunology. "And in some settings, such as endemic pathogens or chronic viral infections, this happens over and over again. That's a lot of proliferation that these T cells undergo in the lifespan of a human."

This raised the question as to why, despite these accelerated rates of proliferation, this [immune response](#) doesn't trigger cancer development.

The answer lies in a T cell's unique ability to defy aging.

Epigenetic markers offer more accurate metrics for age

To study this phenomenon, the researchers made use of specific biomarkers known as [epigenetic markers](#) that accumulate over time. Like counting the rings on a tree stump in a forest, this 'epigenetic clock' tells a retrospective story about the life cycle of a cell independent of the organism itself. The accumulation of genetic mutations, the shortening

of telomeres (the protective caps on chromosomes) and methylation patterns are currently regarded as the most accurate ways to interrogate the process of aging.

The researchers saw this as an ideal way to investigate the curious case of T cell aging. "We started asking questions about what the hallmarks of aging are, specifically the epigenetic hallmarks, and how these can be applied to long-lived T cells," he said. "One of the big questions we had was whether these epigenetic clocks are bound by the lifespan of the organism or not."

Model shows T cells can outlive their origin organism

Through a collaboration with co-corresponding author David Masopust, Ph.D., University of Minnesota, the researchers found the perfect model to address their questions. This model used the same line of T cells through several mouse life cycles.

"Dr. Masopust started this model assuming the cells would eventually decline, but they didn't, they just kept going," explains Youngblood. "This led to his foundational 10-year mouse study which we subsequently used to address whether organismal lifespan limits constrain epigenetic clocks."

Using this model and an epigenetic clock they developed for T cells, the researchers explored the DNA methylation patterns of T cell lineage. They found that age is just a number, and death is not the end.

"Humans don't live forever. But in this case, we could test that concept for T cells," Youngblood said. "Is there an end to an epigenetic clock? Does it plateau? And it didn't for up to four lifetimes, it just kept counting, which was incredible. These cells are not bound by the reasonable limits of organism lifespan."

Cancerous T cells appear hundreds of years old

Next, the researchers determined what happened under conditions of rapid and prolonged proliferation such as in cancer. The team interrogated the T cells of patients with pediatric T-ALL to investigate what happens to their [epigenetic clock](#).

"If epigenetic clocks were linked to the host's chronologic age, then you would expect the T cells from pediatric T-ALL patients to appear young in age," said co-corresponding author Caitlin Zebley, MD, Ph.D., St. Jude Department of Bone Marrow Transplantation & Cellular Therapy. "But our clock predicted these cells to be very old."

From an experiential perspective, the T cells of T-ALL patients appeared to range from 100 to 200 years old. "We think this was related to the fact that they were proliferating so rapidly," Zebley concluded. The T-ALL model offered invaluable insight into the aging process of leukemia cells.

"We were able to use this as a subtraction model from all other programs in leukemia to identify ones that are associated with normal aging and proliferation versus ones that are distinct to leukemia," Youngblood said. "We gained a better idea of which epigenetic programs are associated with leukemia and which are just normal hyperproliferation and aging."

T cell survival is vital to our survival

Considering how active our immune system is, T cell survival is vital to our overall survival. "T cells have so many opportunities to turn cancerous," Youngblood said, "But they can't, otherwise humanity wouldn't exist."

Youngblood, Zebley and Masopust are continuing to study the checks and balances that prevent T cells from undergoing malignant transformation. Through this work, potential therapies that halt, or even reverse, age-related impairments can begin to be considered.

More information: Tian Mi et al, Conserved epigenetic hallmarks of T cell aging during immunity and malignancy, *Nature Aging* (2024).
[DOI: 10.1038/s43587-024-00649-5](https://doi.org/10.1038/s43587-024-00649-5)

Provided by St. Jude Children's Research Hospital

Citation: Age is just a number: Immune cell 'epigenetic clock' ticks independently of organism lifespan (2024, June 12) retrieved 18 June 2024 from
<https://medicalxpress.com/news/2024-06-age-immune-cell-epigenetic-clock.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--