Stabilizing ends of chromosomes could treat age-related disease

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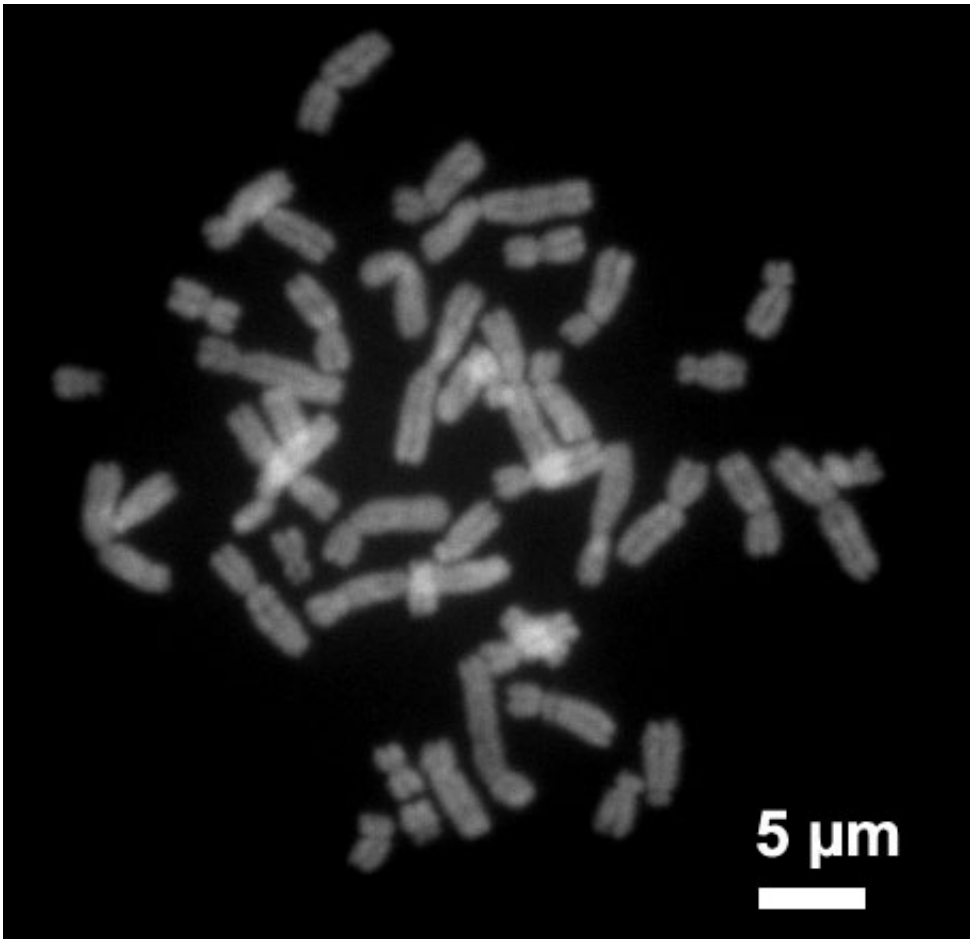

Human chromosomes during metaphase. Credit: Steffen Dietzel/Wikipedia

A study led by researchers at Baylor College of Medicine has uncovered a new strategy that can potentially treat age-related disease and decline.

The study, published in the journal *Cell Metabolism*, demonstrates that shortening of telomeres—the ends of the chromosomes—impairs a class of enzymes called sirtuins, which play an important role in maintaining cell fitness by affecting many metabolic processes and repairing damaged chromosomes. The researchers showed that restoring the activity of sirtuins with a small compound stabilized telomeres and reduced DNA damage, which in turn improved liver disease in a mouse model. These studies suggest that maintaining telomere length might help sustain the regenerative capacity of cells and tissues and improve disease outcome.

"Our genetic material is tightly packed into thread-like structures called chromosomes and at the ends of the chromosomes are particular pieces of DNA called telomeres. Telomeres work like the plastic tips at the end of shoelaces; they prevent chromosomes from unraveling or sticking to each other," said Dr. Ergun Sahin, lead investigator and assistant professor in the Huffington Center on Aging and the Department of Molecular Physiology and Biophysics at Baylor.

Telomeres also are involved in aging and disease; as an organism gets older, telomeres shorten and cells progressively deteriorate, stop dividing and die. Telomere shortening during human aging is believed to be a major underlying cause of age-related decline of stem cells—cells with the potential to develop into many different types of cells and help in the healing process in the body. Telomere shortening also affects the susceptibility of tissues to disease; however, how telomere shortening impairs regeneration and increases risk of disease is not well understood. Evidence suggests that stabilizing telomeres could prevent or slow down aging and disease. In this study, Sahin and his colleagues investigated the effect of restoring telomere length in a mouse model of liver tissue fibrosis

Telomere shortening has been associated with increased risk of organ

failure and tissue fibrosis, usually in liver and lung, as cells with compromised telomeres fail to divide to replace dying cells.

Previous studies have shown that both telomeres and sirtuins contribute to aging and tissue fibrosis and seemed to interact with each other. In this study, Sahin and his colleagues investigated the molecular mechanisms that connected telomeres and sirtuins. For this, they developed a mouse model of liver disease in which the animals were genetically engineered to develop shorter, dysfunctional telomeres and age prematurely. When exposed to certain compounds, these animals quickly develop liver fibrosis—scarring of the liver that over time can lead to cirrhosis.

"In these mice, we discovered that shorter telomeres triggered a reduction in the production of sirtuins in liver and other tissues as well," Sahin said. "Telomere shortening signaled the cell to reduce the production of sirtuins. This observation indicates that telomeres regulate sirtuins."

Interestingly, the researchers also found that in turn, sirtuins can affect telomeres. When Sahin and his colleagues increased the activity of sirtuins by feeding mice a small molecule—nicotinamide mono mononucleotide, or NMN, an NAD+ precursor—telomeres were stabilized.

"Furthermore, feeding NAD+ precursor to the mice not only maintained telomere length but also improved liver condition in these mice," Sahin said.

More research is needed before these findings can be translated into treatments for human conditions.

"It's important to keep in mind that telomere length can also affect

cancer growth. Having shorter telomeres would set cancer cells on a path to self-destruction, but keeping their telomeres long would likely allow them to continue proliferating," Sahin said. "We plan to continue our investigation on the molecular mechanisms involved in the telomere-sirtuin interactions in order to better understand the benefits as well as the potential risks of telomere length manipulation in health and disease."

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