Leibniz Institute on Aging – Fritz Lipmann Institute

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As our gut age: New study finds out why important genes "go quiet" as we get older

Researchers from the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena, Germany, the Molecular Biotechnology Centre (MBC) in Turin and the University of Turin, Italy, have discovered a fundamental mechanism of aging in the gut. Over the course of life, a specific form of epigenetic aging - known as ACCA drift - accumulates in intestinal stem cells. This leads to the shutdown of key genes through hypermethylation. The drift spreads across the intestinal crypts and is caused by a combination of age-related inflammation, weakened Wnt signaling, and impaired iron metabolism, which affects the activity of DNA-modifying enzymes. The findings provide new explanations for why the risk of colorectal cancer increases with age and which molecular processes are involved.

Jena/Turin/Jerusalem. The human gut renews itself faster than any other tissue: every few days, new cells are created from specialized stem cells. However, as we get older, epigenetic changes build up in these stem cells. These are chemical markers on the DNA that act like switches, determining which genes remain active.

The study, recently published in *Nature Aging*, was conducted by an international team led by Prof. Francesco Neri from the University of Turin, Italy, and shows that changes in the gut do not occur randomly. Rather, a specific pattern develops over the course of aging, which the researchers refer to as ACCA (Aging- and Colon Cancer-Associated) drift. "We observe an epigenetic pattern that becomes increasingly apparent with age," explains Prof. Neri, former group leader at the Leibniz Institute on Aging - Fritz Lipmann Institute in Jena.

Genes that maintain the balance in healthy tissue are particularly affected, including those that control the renewal of the intestinal epithelium via the Wnt signaling pathway. The changes described as "drifting" can be detected not only in the aging gut, but also in almost all colon cancer samples examined. This suggests that the aging of stem cells creates an environment that promotes the development of cancer.

Patchwork of aging: Different areas of tissue are affected differently

The fact that the drift is not evenly distributed throughout the intestine is particularly noteworthy. Each intestinal crypt—a small, tubular section of the intestinal mucosa—originates from a single stem cell. When this stem cell undergoes epigenetic changes, the entire crypt takes on these changes. Dr. Anna Krepelova explains the process as follows: "Over time, more and more areas with an older epigenetic profile develop in the tissue. Through the natural process of crypt division, these regions continuously enlarge and can continue to grow over many years."

This explains why the intestines of older people contain a veritable patchwork of crypts that have remained young and others that have aged significantly, and why certain regions are particularly susceptible to producing more degenerated cells, which promotes cancer growth.

Impaired iron metabolism shuts down repair systems

Why does this drift occur? Researchers have shown that older intestinal cells absorb less iron but release more iron at the same time. This reduces the amount of available iron (II) in the cell nucleus, which serves as a cofactor for the TET (ten-eleven translocation) enzymes. These enzymes normally protect from the excess DNA methylations, but if the cell doesn't have enough iron, they can't do their job properly. Excess DNA methylations are no longer broken down.

"When there's not enough iron in the cells, faulty markings remain on the DNA. And the cells lose their ability to remove these markings," explains Dr. Anna Krepelova. This has a kind of domino effect: as the TET activity decreases, more and more DNA methylations accumulate, and important genes are switched off; they "fall silent." This can further accelerate epigenetic drift.

Inflammation and impaired Wnt signaling accelerate aging

The research team was also able to demonstrate that mild inflammatory processes in the gut associated with aging further reinforce this mechanism. Inflammatory signals alter iron distribution in the cell and put strain on the metabolism. At the same time, Wnt signaling also weakens—a signaling pathway that is important for keeping stem cells active and functional.

This combination of iron deficiency, inflammation, and Wnt signaling loss acts as an "accelerator" of epigenetic drift. As a result, the aging process in the intestine can begin earlier and spread faster than previously thought.

Aging drift can be influenced

Despite the complexity of the mechanism, the study also provides encouraging results. The researchers succeeded in slowing down or partially reversing epigenetic drift in organoid cultures—miniature intestinal models grown from intestinal stem cells—by restoring iron import or specifically activating the Wnt signaling pathway.

Both measures led to the TET enzymes becoming more active again and the cells starting to break down the methylations once more. "This means that epigenetic aging does not have to be a fixed, final state," emphasizes Dr. Anna Krepelova. "For the first time, we are seeing that it is possible to tweak the parameters of aging that lie deep within the molecular core of the cell."

Publication

Anna Krepelova, Mahdi Rasa, Francesco Annunziata, Jing Lu, Chiara Giannuzzi, Omid Omrani, Elisabeth Wyart, Paolo Ettore Porporato, Ihab Ansari, Dor Bilenko, Yehudit Bergman & Francesco Neri. Iron homeostasis and cell clonality drive cancer-associated intestinal DNA methylation drift in aging. Nat Aging (2025). https://doi.org/10.1038/s43587-025-01021-x

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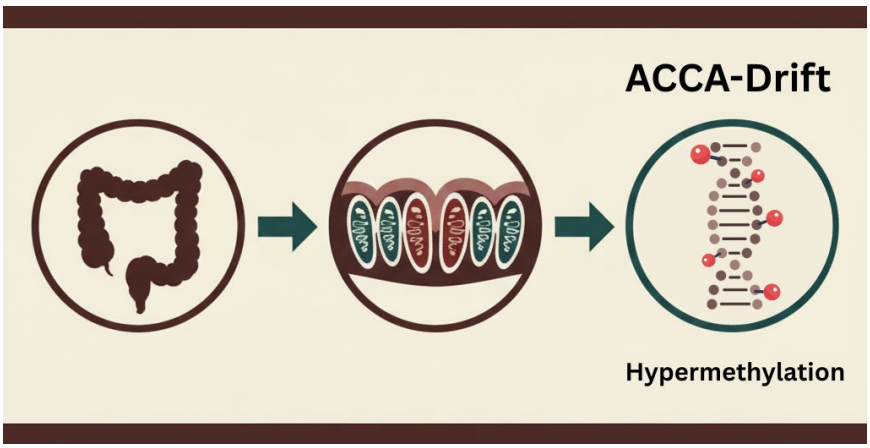
Picture



In older intestines, the ACCA drift, an increase in DNA hypermethylation in intestinal stem cells, leads to the shutdown of important genes. This limits the self-renewal of intestinal crypts and reduces the tissue's ability to regenerate, which significantly increases the risk of colon cancer in older age. (Picture: FLI / Kerstin Wagner)

Background

The Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena is a federal and state government-funded research institute and member of the Leibniz Association (Leibniz-Gemeinschaft). FLI conducts internationally recognized, high-impact research on the biology of aging at the molecular, cellular, and systems levels. Scientists from around 40 countries investigate the mechanisms of aging to uncover its root causes and pave the way for strategies that promote healthy aging. Further information: www.leibniz-fli.de.

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