Selfish genetic elements amplify inflammation and age-related diseases

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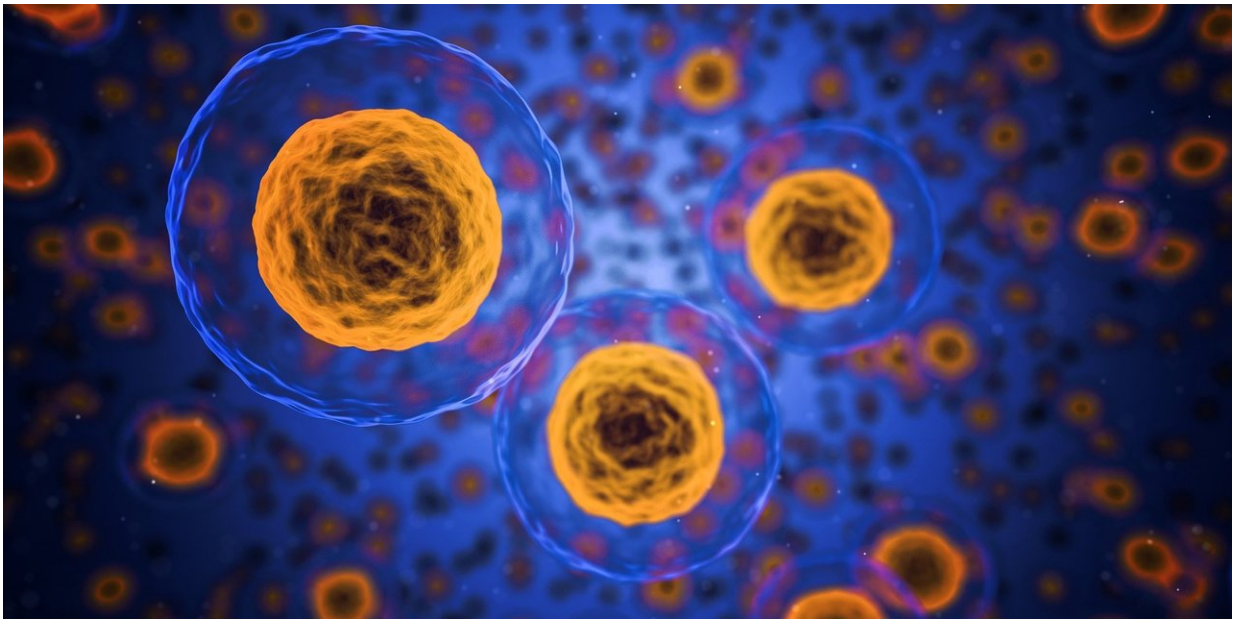

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Aging affects every living organism, but the molecular processes that contribute to aging remain a subject of debate. While many things contribute to the aging process, one common theme in animal aging is inflammation—and this may be amplified by a class of selfish genetic elements.

The human genome is littered with selfish genetic elements—repetitive

elements that do not seem to benefit their hosts, but instead seek only to propagate themselves by inserting new copies into their host genomes. A class of selfish genetic elements called LINE1 retrotransposons are the most prevalent retrotransposon selfish genetic elements found in humans; approximately 20 percent of both human and mice genomes are composed of LINE1s.

Researchers have long suspected that LINE1s contribute to cancer and genomic instability. However, the harm inflicted by these genomic parasites reaches much further than researchers had at first thought. In a paper in the journal *Cell Metabolism*, researchers from the University of Rochester, including Vera Gorbunova, the Doris Johns Cherry professor of biology, and Andrei Seluanov, professor of biology, show that LINE1 retrotransposons become more active with age and may cause age-related diseases by triggering inflammation. By understanding the impacts of retrotransposons, researchers can better recognize the processes by which cells age and how to combat the deleterious effects of aging.

Human cells have evolved multiple molecular mechanisms—such as gene silencing—to keep selfish genetic elements like LINE1s at bay. However, these mechanisms become less efficient during the aging process, allowing LINE1 elements to be reactivated.

As LINE1s become active, some of their copies leak outside the cell nucleus into the cytoplasm, Gorbunova says. "Any DNA in the cytoplasm is a signal for alarm, as it resembles viruses that are invading the cell." Cytoplasmic "guardians"—types of DNA sensors—typically recognize invaders and trigger immune responses like inflammation. This process, which normally functions to protect humans from viruses and foreign DNA, recognizes leaked LINE1 copies in the old cells and triggers a "false alarm" in the form of age-related inflammation.

The researchers found that they can reduce LINE1s using drugs that inhibit reverse transcriptase, an enzyme that catalyzes LINE 1 DNA formation. These drugs were originally developed to combate reverse transcriptase in HIV patients. Using these drugs to reduce LINE1s improves health in mice and reduces inflammation, in addition to improving lifespan, Seluanov says. "Sterile inflammation triggered by LINE1 elements is a new mechanism of aging. We can now develop strategies that target LINE1s and the pathways that lead to inflammation."

With these new insights into LINE1 and its effects on inflammation, researchers hope to develop interventions aimed at inhibiting LINE1s, Gorbunova says. "These interventions may serve as new forms of therapy for age-related diseases fueled by inflammation, such as neurodegeneration, cancer, diabetes, and autoimmune diseases."

More information: Matthew Simon et al, LINE1 Derepression in Aged Wild-Type and SIRT6-Deficient Mice Drives Inflammation, *Cell Metabolism* (2019). DOI: 10.1016/j.cmet.2019.02.014

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