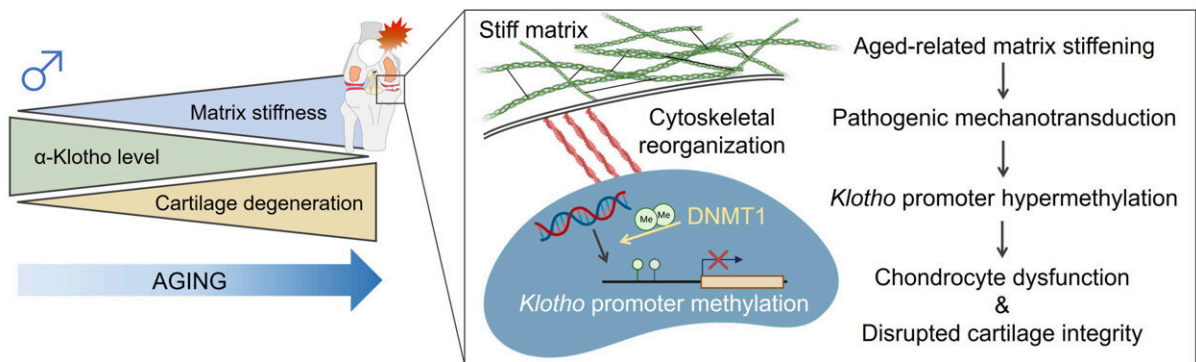


New mechanism uncovered behind osteoarthritis could inform new treatments

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Age-related matrix stiffening in articular cartilage initiates pathogenic mechanotransductive signaling, driving chondrocyte dysfunction as well as disrupted cartilage integrity through Klotho promoter hypermethylation. Portions of the figure were created with biorender.com. Credit: Ambrosio et al, *Nature Communications*

Researchers in the United States and Japan have discovered a new mechanism that links age-related cartilage tissue stiffening with the repression of a key protein associated with longevity. These findings enhance the understanding of mechanisms that lead to the deterioration of joints that causes osteoarthritis, according to the authors of a new study, published January 10th in *Nature Communications*.

In the study, researchers showed that increased stiffening of the extracellular matrix—a network of proteins and other molecules that surround and support tissues in the body—led to a decrease in a so-called "longevity protein" called Klotho (α -Klotho) in knee cartilage brought about by epigenetic changes. This Klotho decrease then damaged the cells in healthy cartilage called chondrocytes. Conversely, exposing aged chondrocytes to a softer extracellular matrix restored the knee cartilage to a more youthful state.

As stiffening of extracellular matrix is a defining feature of cartilage aging, these findings demonstrate the role Klotho plays in the formation of [osteoarthritis](#) and offers new potential treatment targets to restore cartilage health. The researchers also note that their results may be applicable to the toll that epigenetic factors caused by aging takes on other tissues throughout the body.

"This research enhances our mechanistic understanding of why osteoarthritis happens in the first place, and it paves the way for the development of therapeutics to prevent these changes. Such therapeutics are important because there are currently no disease-modifying treatments for osteoarthritis; the best we can do for now is minimize pain and disability," said Fabrisia Ambrosio, Ph.D., MPT, inaugural director of the Atlantic Charter Discovery Center for Musculoskeletal Recovery of the Schoen Adams Research Institute at Spaulding Rehabilitation Network, and Member of the Faculty of Physical Medicine and Rehabilitation at Harvard Medical School. "Since matrix stiffening is a feature of aged tissues throughout the body, we anticipate that these findings may also have implications beyond cartilage repair for the field of aging research."

Examining the root cause of irreversible cartilage damage

Osteoarthritis occurs when cartilage in a joint stiffens and begins to break down which then damages the underlying bone, resulting in pain, swelling and feelings of stiffness. Osteoarthritis is the most common form of arthritis, affecting approximately 32.5 million individuals in the United States alone—rates expected to rise with the [aging population](#) and trends in obesity. Osteoarthritis can significantly interfere with a person's ability to perform routine daily tasks; about half of adults with the condition are of working age, which impacts their ability to earn a living.

There are currently no treatments to reverse this cartilage stiffening and resulting damage. Treatments such as exercise, [weight loss](#), physical therapy, medications, injections and joint replacement surgery are aimed at reducing pain and improving mobility. Much has remained unknown about the molecular causes of this damage and how to treat it. These unknowns are especially germane to knee osteoarthritis, where no single event causes the cartilage damage, and the greatest predictive risk factor is aging.

Increasingly, researchers have sought to better understand the role epigenetics, or how changes in behaviors and environment as people age alter how genes work, can impact tissues and disease processes throughout the body.

Using advanced mass spectrometry technology, the researchers mapped out the trajectory of structural and protein changes in mice with knee osteoarthritis over the course of their lifetimes and according to sex. They then compared their findings to the current understanding of knee osteoarthritis in humans.

The researchers found that Klotho was heavily involved in the molecular process that led to osteoarthritis. This work was an extension of previous studies showing that Klotho protects mitochondria within skeletal muscle

and plays a key role in skeletal muscle regeneration following injury. As people age, their klotho levels go down, hence why it's referred to as a longevity protein.

The new analysis revealed that when [knee cartilage](#) tissue became stiffer, the gene that codes for Klotho was repressed. They verified this in models of young and old chondrocyte cells responsible for cartilage formation, which were seeded in environments designed to mimic young and old tissue stiffness. Young chondrocyte cells looked old when put on a stiff surface due to the loss of Klotho, but when the researchers protected the cells from the stiffness in their environment, they observed chondrocyte health.

"These results provide a compelling new paradigm that will be important for the field in terms of understanding the connection between age-related tissue stiffening and risk for osteoarthritis with aging," said Hirotaka Iijima, Ph.D., PT, assistant professor at Institute for Advanced Research and Graduate School of Medicine in Nagoya University.

Interestingly, their analysis also revealed that incidence of osteoarthritis increased in male mice with age, while female mice showed no onset of the disease and their [cartilage](#) tissue was generally preserved. This unexpected finding differs from the response observed in people, where post-menopausal women are significantly more likely to develop severe knee osteoarthritis than men. These findings warrant further study, according to the authors, and a project is underway in Dr. Ambrosio's lab to examine the effects menopause has on knee osteoarthritis at the molecular level.

Future research aims to address therapeutic gaps in age-related conditions

With the latest findings, the researchers plan to study whether there are ways to intervene with the disease process that leads to osteoarthritis, such as by blocking the pathway that represses Klotho, even in the face of a stiff extracellular matrix environment. They hope their findings can be used to develop treatments for osteoarthritis and other conditions caused by aging.

"We're interested in evaluating whether epigenetic regulation of Klotho and other longevity factors by the extracellular matrix may help explain functional decline of tissues throughout the system," said Dr. Ambrosio.

In addition to Drs. Ambrosio and Iijima, co-authors of the study include Gabrielle Gilmer, BCE, Kai Wang, Ph.D., Allison C. Bean, MD, Ph.D., Yuchen He, Hang Lin, Ph.D., Wan-Yee Tang, Ph.D., Daniel Lamont, Ph.D., Chia Tai, MS, Akira Ito, Ph.D., PT, Jeffrey J Jones, Ph.D. and Christopher Evans, Ph.D.

More information: Age-related matrix stiffening epigenetically regulates α -Klotho expression and compromises chondrocyte integrity, *Nature Communications* (2023). [DOI: 10.1038/s41467-022-35359-2](https://doi.org/10.1038/s41467-022-35359-2)

Provided by Mass General Brigham

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