The locked library: Tendinosis causes cells to reorder their DNA incorrectly

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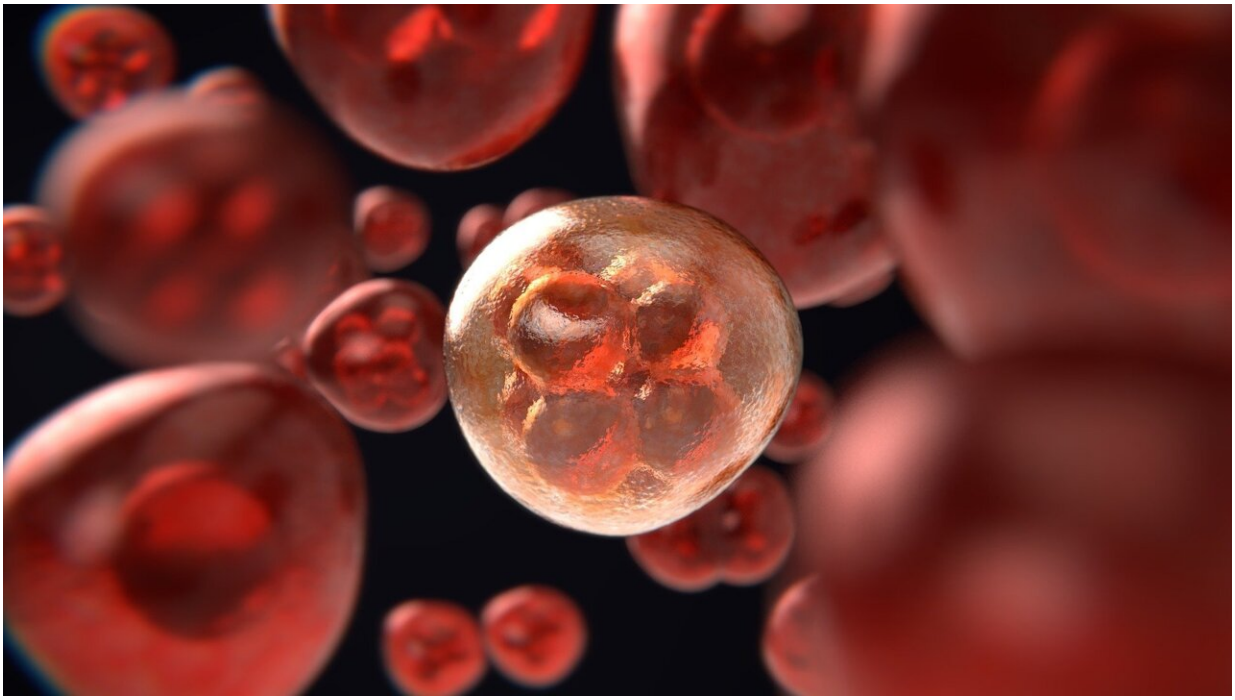

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Imagine you're trying to do a job and all of the information you need to do it is in a few books at the library. Except, those books are randomly arranged along with all the other books on shelves across the whole building. Without that vital information from the books you were looking for, you wouldn't perform your job very well.

This is the situation that researchers at the Perelman School of Medicine at the University of Pennsylvania found when they studied the nucleus of cells inside connective tissues deteriorating as a result of tendinosis. Disease-related disruptions in the environments that cells exist in caused the re-organization of the genome—which is the sum of an organism's DNA sequences—inside the cell's nucleus, changing the way cells functioned and making them unable to reorder their DNA information in the right way again. These findings, published today in *Nature Biomedical Engineering*, point to the possibility of new treatments—such as small-molecule therapies—to bring in a sort of librarian that could restore order to the affected cells.

"This is really important because the research tells us, for the first time, that diseased connective tissue cells change the physical structure of their genomes and stop responding to normal physical cues from their environment," said the study's lead author, Su Chin Heo, Ph.D., an assistant professor of orthopedic surgery. "If we can figure out exactly why this happens, we might be able to 'unlock' the diseased state of these cells, and bring them back toward a healthy state."

Microscale changes in the environments that cells exist in have macro-level effects because of the way they change cell behaviors and how a body functions. But this dynamic is not well understood. So Heo and colleagues set out to examine how cells in degenerating connective tissue respond to changes in their physical environment and, particularly, how the spatial organization of chromatin—the material that DNA is made out of, which has been shown to differ based on cell type—might be affected by changes brought on by disease.

To do this, the team used the latest super-resolution imaging techniques to observe human cell models, specifically tenocytes (tendon cells involved in maintaining the tissue's structure) and mesenchymal stromal cells (similar to stem cells, they can become a variety of cells needed to

build or maintain tissue).

In these models, the researchers observed that chemical and mechanical changes within environments mimicking degenerating tendons resulted in tenocytes improperly re-ordering their chromatin. And even when the researchers presented these cells with the proper mechanical environment, they saw that the cells had lost their ability to properly re-organize their genome back to a normal state—the cells could no longer respond correctly. Cells that were healthy responded well to the same chemical and mechanical prompts, so it seems that the diseased cells forgot what they were doing, or couldn't access the right information in their crisis response.

"While we discovered that cells in diseased microenvironments lose their epigenetic memory, these results also suggest that epigenetic treatments—like small molecule medications—could restore healthy genome organization and may prove effective treatments in conditions affecting dense tissues," said the study's senior author, Melike Lakadamyali, Ph.D., an associate professor of physiology. "That's something that we plan to follow up on and test."

The researchers already have secured grants studying whether cartilage cells and meniscus cells are affected similarly by disease-disrupted genomes. They're also studying whether the aging process has a similar effect.

"Once we understand these and the specific cellular processes that makes them happen—what locks the library door—we can use small molecule drugs as skeleton keys to either try to stop it from happening or reverse the process," said study co-senior-author Robert Mauck, Ph.D., a professor of orthopedic surgery and director of Penn's McKay Orthopedic Research Laboratory.

More information: Robert Mauck, Aberrant chromatin reorganization in cells from diseased fibrous connective tissue in response to altered chemomechanical cues, *Nature Biomedical Engineering* (2022). DOI: 10.1038/s41551-022-00910-5. www.nature.com/articles/s41551-022-00910-5

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