Researchers probe cell nucleus response with needle-tip technique

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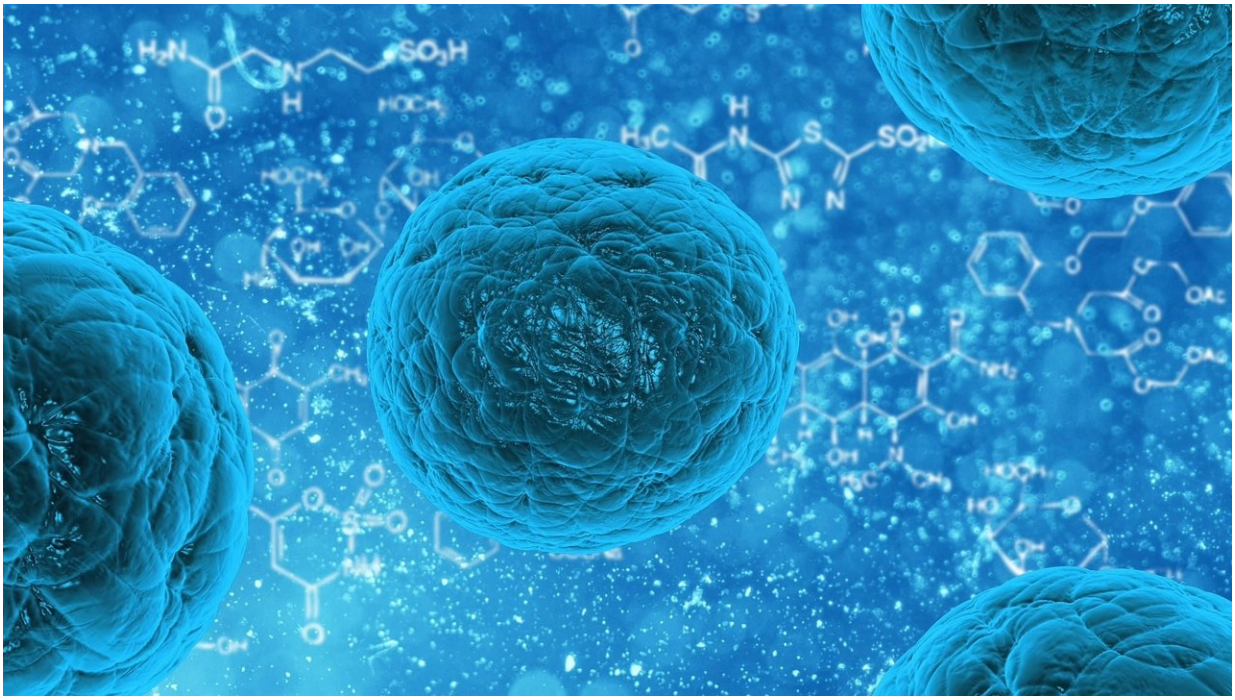

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Kaitlin McCreery is the coauthor of a new paper published in *Small* that deals with diagnosing diseases such as osteoarthritis in soft tissue. McCreery is currently a Ph.D. student in the Neu Lab where she studies the biophysical relationship between cells and tissues to gain insights about tissue development and pathology. The work is one of two papers on nuclear mechanobiology that were published in January by the Neu

lab. The other paper was also published in *Small* and led by Soham Ghosh.

We asked her about possible applications of the work, life in the Neu lab and where the research goes from here.

Question: How would you describe the work and results of this paper to a high school student? What are the applications in the real world?

Answer: There are many diseases in which tissues experience a cascading decline in function for which there are no current solutions. Osteoarthritis—a common disease of cartilage degradation—is one example. Understanding tissue pathology on multiple scales—and specifically how changes in tissues are propagated to the cell nucleus that houses your DNA—will help us develop solutions in regenerative medicine that manipulate the form and function of cells.

Cells are physically linked to a network of proteins around them, which allows them to sense and respond to mechanical cues like pushing and pulling from their immediate environment. We developed an experimental technique to directly probe the mechanical properties of the nucleus with a very small needle. We combined fluorescent microscopy with atomic force microscopy to measure stiffness of nuclear, cell and the local matrix without disrupting their interactions. We found that the cartilage cell nucleus becomes less stiff when the native cartilage tissue environment is disrupted with enzymes. The nucleus can change its physical properties to match the surrounding tissue, perhaps to maintain homeostasis or control what genes are activated in response to stimuli. The nucleus is not commonly thought to be a dynamic structure, so these findings are really interesting and relevant in a lot of ways to the overall discussion.

Q: Is this a research topic or area you were interested in before joining the Neu lab?

A: In the Neu lab, researchers come from a variety of interdisciplinary backgrounds which helps us ask biological questions from a different perspective as physicists and engineers. Before I began working here, I studied physics and mechanical engineering and explored biological topics on the side. I joined because I want to apply my technical approach to make an impact on tissue regeneration in medicine.

Q: Was there a particular aspect of this work that was hard to complete?

A: As one of our reviewers put it, "the challenging nature of this work is important." Just imagine how we collected this data. First, we took a live piece of tissue and then poked a cell nucleus with a nanoscale needle. Talk about a difficult bull's-eye to hit consistently!

And then overall, asking questions in nuclear mechanobiology is difficult because the field is still developing new methods to investigate the mechanical properties of the nucleus and understanding its implications. For me, I am driven by that, though, because I want to study biological systems from a physics engineering approach.

Q: What research questions are still to be answered after this paper?

A: This study is only the beginning to investigate multiscale tissue function and pathology. The main advantage of our AFM needle-tip technique is that we can use it to gain insight into nuclear mechanisms during tissue development, disease and regeneration.

Q: How has studying at CU Boulder shaped your research and career?

A: It is an exciting time to be a biomedical engineer! The research culture here at CU Boulder is highly collaborative between research groups to accomplish novel interdisciplinary science. Biological questions about development and disease are immensely complex, especially at the smallest scales of the cell and nucleus. These hard questions require scientists to work across traditional disciplines to solve major challenges in engineering and medicine, which is an integral part of research at CU Boulder.

More information: Kaitlin P. McCreery et al. Nuclear Stiffness Decreases with Disruption of the Extracellular Matrix in Living Tissues, *Small* (2021). DOI: 10.1002/smll.202006699

Soham Ghosh et al. Image-Based Elastography of Heterochromatin and Euchromatin Domains in the Deforming Cell Nucleus, *Small* (2021). DOI: 10.1002/smll.202006109

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