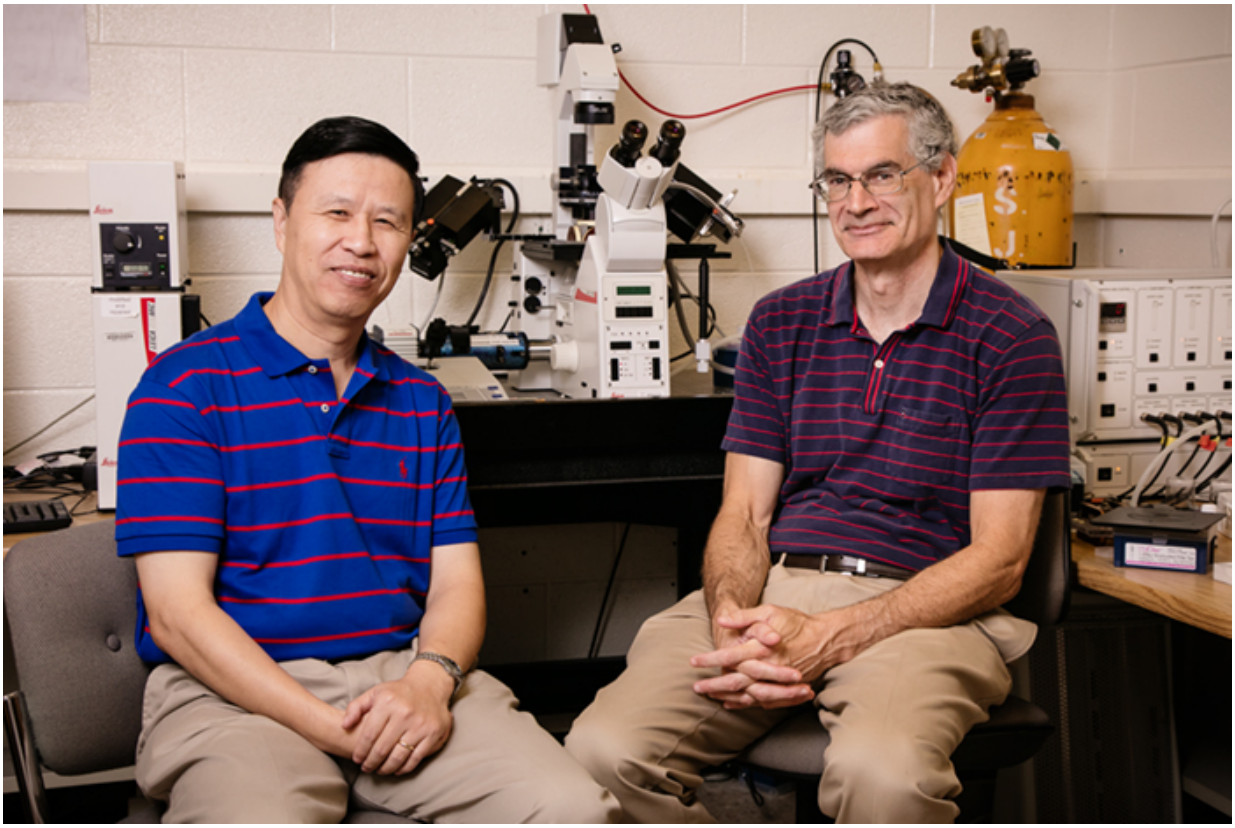
Force triggers gene expression by stretching chromatin

August 26 2016



Professors Ning Wang and Andrew Belmont led a team that found the pathway by which physical forces drive gene expression in cells. Credit: L. Brian Stauffer

How genes in our DNA are expressed into traits within a cell is a complicated mystery with many players, the main suspects being

chemical. However, a new study by University of Illinois researchers and collaborators in China has demonstrated that external mechanical force can directly regulate gene expression. The study also identified the pathway that conveys the force from the outside of the cell into the nucleus.

Identifying the ways mechanical forces send signals within cells has applications not only in fundamental cell biology, but also for cancer, stem cells and regenerative medicine, said mechanical science and engineering professor Ning Wang, who led the study with cell and developmental biology professor Andrew Belmont. The researchers published their work in the journal *Nature Materials*.

"Each cell in your body has the same DNA, but tissues behave very differently because genes are expressed differently," Wang said. "There is so much we don't know about gene expression. I think this work is the beginning to unravel some of the unknowns."

Researchers have long known that forces, both external and internal, can affect cell behavior. But the question loomed as to whether the forces themselves triggered changes in gene expression, or if the forces triggered a chemical-signaling pathway within the cell.

"Cells only have two 'senses' to interact with their environment," Wang said. "They cannot see or hear, but they can 'feel' mechanical forces and 'taste' chemical signals. Many studies have detailed chemical-signaling pathways, but it's important to understand how the mechanical forces affect the cell as well. Mechanical signaling is as important as chemical signaling, and this study shows it's a direct pathway."

The researchers stuck tiny magnetic beads to proteins attached to the external membranes of hamster cells. They were able to change the direction and angle of the force the beads exerted while maintaining a

consistent magnitude of the force, and found that the external force directly caused regions of chromatin in the nucleus to stretch out. Chromatin is the condensed DNA and protein mixture that makes up chromosomes. Using advanced imaging techniques, the researchers found an increase in transcription of the genes in the stretched regions.

"Work extending back decades has correlated chromosome decondensation with increased gene expression, but it has been extremely difficult to distinguish cause and effect," Belmont said. "Does gene activity cause chromatin to decondense, or does decondensation actually drive increased gene expression? Here, we saw chromatin stretching directly drive increased gene expression, which provides a mechanically based mechanism for cells to sense their environment."

The degree of stretching and therefore gene expression varied based on the direction of the force in relation to the cell's cytoskeleton, the internal framework of protein tubes that supports the cell.

"The actin in the cytoskeleton forms bundles. When the force is perpendicular to the bundles, it's like plucking violin strings," Wang said. "It's incredibly tense, and the signal is transferred through the cytoskeleton to the nucleus and stretches the chromatin. Doing it the other way, along the string direction, there isn't much vibration, so a force of the same magnitude has less effect. The effect gets stronger the closer the angle gets to 90 degrees."

The researchers were able to follow the force and identify the pathway that it travels along the cytoskeleton to the chromatin in the nucleus. Knowing the pathway is important, Wang said, because researchers can now explore mechanical signaling in more detail and perhaps develop ways to harness it for gene regulation or identify targets for cancer therapies.

For example, Wang's group has published several studies detailing the unique mechanical properties of tumor-repopulating cells—cancer cells that evade standard drug therapies and tend to slip away to metastasize in new locations. He hopes that this study opens new avenues of attack to disable tumor-repopulating cells with fewer side effects than traditional cancer treatments.

Now that they've detailed how forces affect stretching of the chromatin, the researchers are beginning to look at how forces affect chromatin compression and what that means for gene expression. They are also probing further into other factors regulating gene expression when the chromatin is stretched.

"When we apply these forces, why are some genes activated while some are not? We think there are factors that inhibit, so that some genes are not ready to be force-activated," Wang said.

More information: Arash Tajik et al, Transcription upregulation via force-induced direct stretching of chromatin, *Nature Materials* (2016). DOI: 10.1038/nmat4729

Provided by University of Illinois at Urbana-Champaign