Shape-shifting nucleosomes open new avenues for epigenetics research

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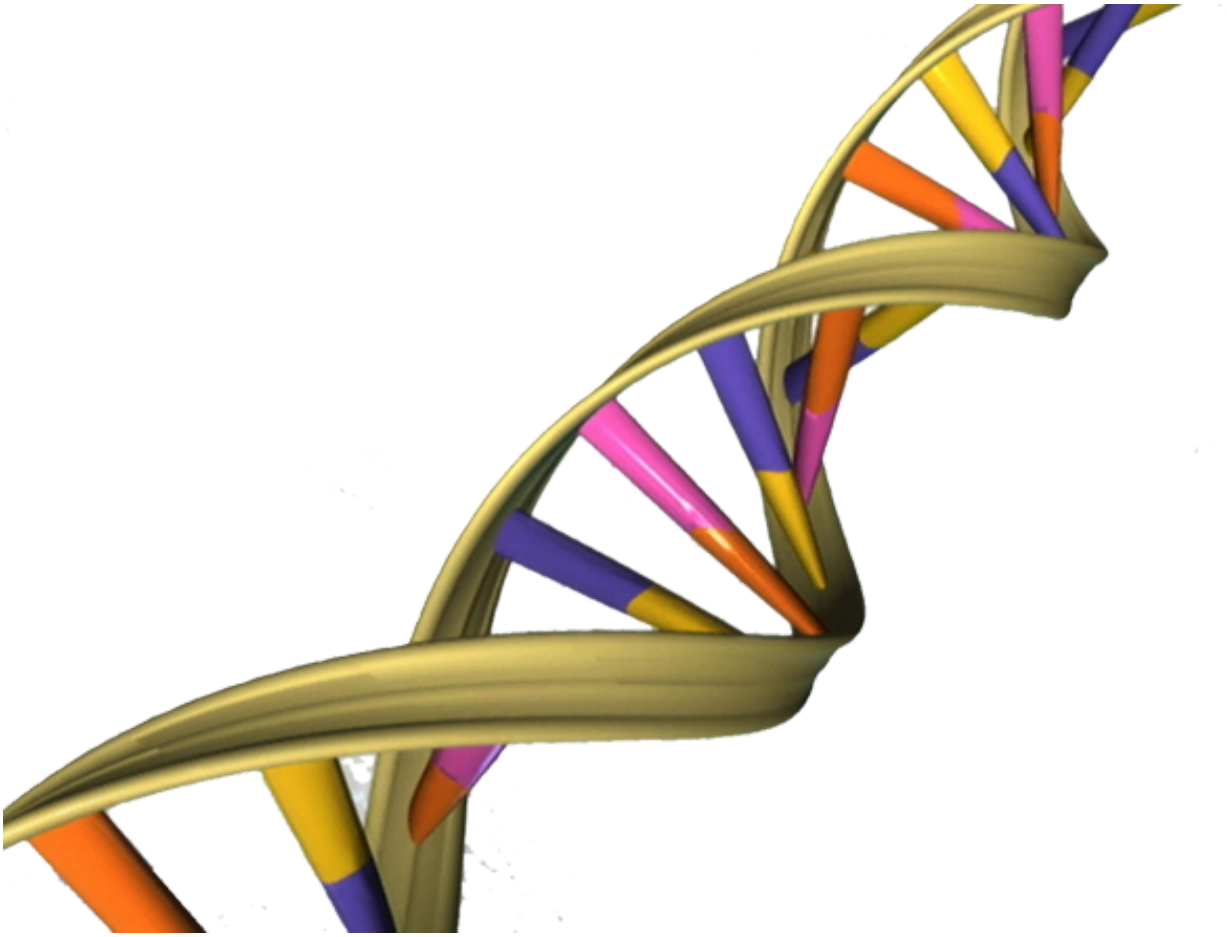

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

The textbook description of chromatin, the condensed form DNA takes when it is not in use, consists of rigid building-blocks called nucleosomes, which act as spindles on which inactive DNA can be spooled and archived. But a new UCSF study promises to overturn this understanding, demonstrating that nucleosomes actively change their shape as part of the larger process of epigenetic regulation of gene expression.

The new study—published online January 19, 2017 in *Science*—suggests that the biology that controls which regions of DNA are read out, and when, may be much more complex than previously believed.

The research was led by Kalyan K. Sinha, PhD, a postdoctoral researcher in the lab of senior author Geeta J. Narlikar, PhD, professor of biochemistry and biophysics at UCSF, in collaboration with co-senior author John D. Gross, PhD, a professor of pharmaceutical chemistry at UCSF.

New Evidence Could Explain Gene Regulation

Epigenetics—the study of genome modifications that control cell fate, some of which are thought to reflect environmental influences on the genetics of health and disease—is one of the key frontiers of modern genomics. At the heart of epigenetics is the question of how cells control which stretches of DNA are accessible to be read out and translated into proteins, and which sequences are spooled away and archived on nucleosomes.

The dominant model in the field portrays nucleosomes as passive spindles, themselves 'octamers' made up of eight blocks of rigid histone proteins that snap together like Lego pieces when wrapped in DNA, and which must break apart or slide out of the way to allow their archived DNA to become active again. But Sinha, Gross and Narlikar's new study

promises to change this paradigm, demonstrating that nucleosomes are capable of shifting like putty in response to as-yet unknown signals.

"The field of epigenetics may have been literally scratching the surface," Narlikar said, referring to the field's focus on the function of epigenetic "marks," such as the chemical tags called methyl groups, on the exposed surfaces of histone proteins. "Altering the shape of the nucleosome, a fundamental building block of the chromosome, could in principle have large effects on processes ranging from genome organization to epigenetic inheritance."

In particular, according to Narlikar, a malleable nucleosome would make it possible for cells to read out segments of DNA without completely disassembling the nucleosome. This offers a potential explanation for mysterious histone modifications that would be buried uselessly deep inside the nucleosome according to the traditional model, and suggests a new mechanism for the extreme compaction chromosomes undergo during cell division, and offers potential answers to the chicken-and-egg problem of how cells know how to pull specific DNA sequences out of the archives without being first able to "see" them.

"If you look at crystal structures of the conventional model of the nucleosome, there's no slack, no room for the DNA to be pulled out. To read the DNA, you would have to move the whole histone octamer out of the way," Narlikar said. "What we're seeing is that you can keep them in place and still expose the DNA by changing the shape of the nucleosome."

In some ways, the authors say, the fact that nucleosomes are dynamic rather than static makes a lot of sense biologically:

"As a protein biochemist who had studied the amazing plasticity many proteins display, the idea of a completely static histone octamer was a

little disconcerting," Sinha said. "It had seemed to me for some time that a nucleosome capable of adopting alternate conformations in response to its surrounding molecular environment could more efficiently ensure the structural integrity and fluidity chromatin needs for its biological role. I'm very grateful that Geeta and John shared my interest in pursuing this question."

New Imaging Techniques

The new discovery was made possible by a new and technically challenging nuclear magnetic resonance (NMR) method, which discerns features of chromatin dynamics that are invisible to other commonly used approaches. The technique revealed changes in how histones contact one another, demonstrating convincingly that nucleosomes are dynamic, rather than rigid.

Gross credits the spark of the new discovery to a fortuitous conversation between himself, Narlikar, and the late Jonathan Widom of Northwestern University following a UCSF seminar. "The best collaborations are formed by people who are not afraid of strange or unusual ideas," Gross said. "Jonathan was inspirational to me because he looked at chromatin structure and dynamics like a physical chemist, bridging biological and structural worlds."

In describing the work, Narlikar quoted Proust, who wrote, "The only true voyage of discovery, … would be not to visit strange lands but to possess other eyes, to behold the universe through the eyes of another…."

"The new NMR approach literally allowed us to look with 'other eyes,' and in doing so allowed us to discover a fundamental new property of chromatin," Narlikar said.

Much is still unknown, Narlikar said, about the details of nucleosomes' shape-shifting abilities, as well as what types of cellular biochemical signals regulate their dynamics, and exactly what effects these changes have on DNA regulation. "All of these ideas are speculative at this point. But we wouldn't have had the conceptual framework to think of any of these hypotheses until there was reason to think of the nucleosome as dynamic rather than rigid. The number of questions this opens up is incredibly exciting."

More information: Kalyan K. Sinha et al. Distortion of histone octamer core promotes nucleosome mobilization by a chromatin remodeler, *Science* (2017). DOI: 10.1126/science.aaa3761

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