From strands to droplets—new insights into DNA control

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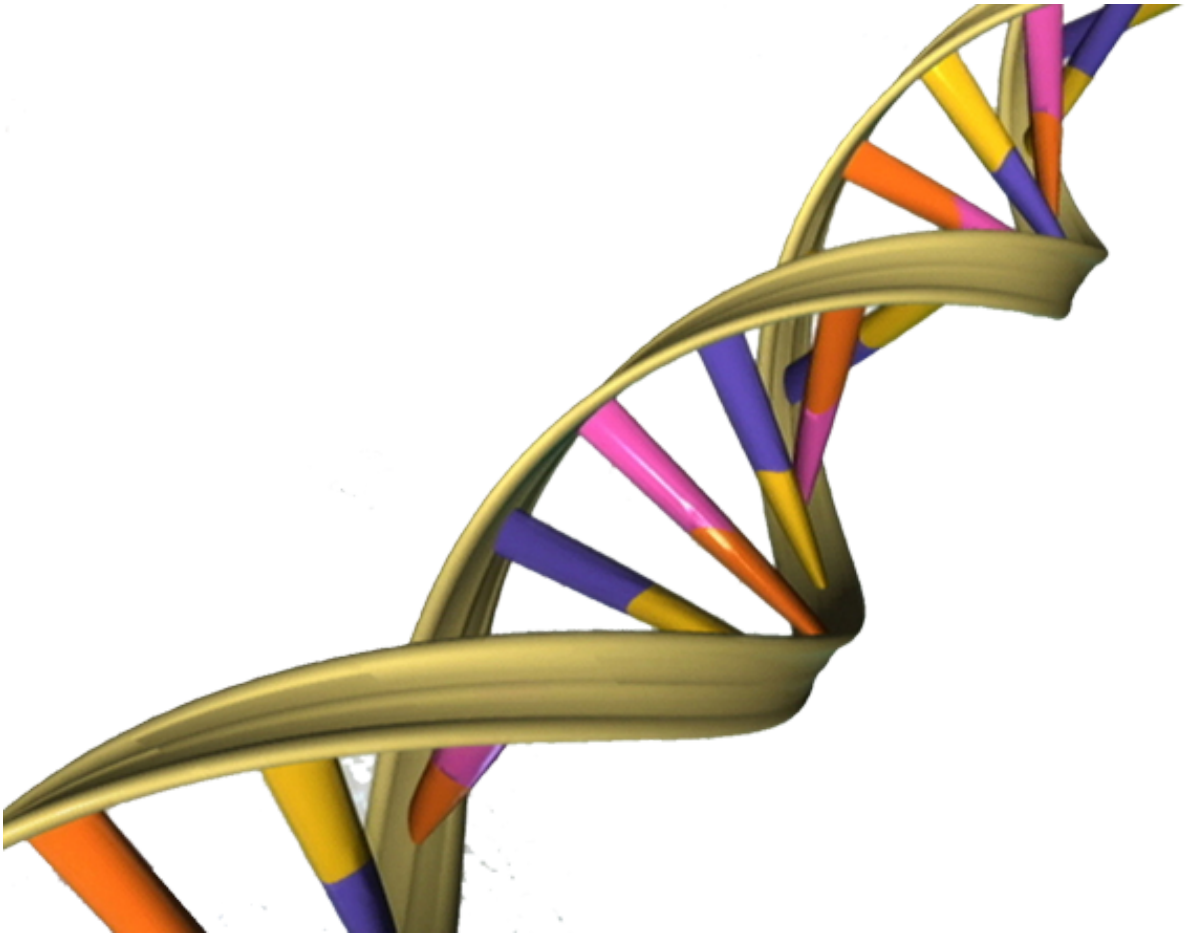

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A host of proteins and other molecules sit on the strands of our DNA, controlling which genes are read out and used by cells and which remain silent. This aggregation of genetic material and controlling molecules, called chromatin, makes up the chromosomes in our cell nuclei; its control over which genes are expressed – or not – is what determines the difference between a skin cell and a neuron, and often between a healthy cell and a cancerous one.

Parts of the genome are only loosely coiled in the nucleus, allowing cells to access the genes inside, but large sections are compacted very densely, preventing the genes form being read until their region of the genome is unfolded again. These compacted regions, known as heterochromatin, are formed by a protein known as HP1α and similar proteins, but exactly how HP1α segregates this off-limits DNA from the rest of the nucleus has been largely a mystery, until now.

In a new study by UC San Francisco researchers published in the journal *Nature* on June 22, 2017, what looked at first like a failed experiment instead revealed the intriguing possibility that HP1α binds to stretches of DNA and pulls it into droplets that shield the genetic material inside from the molecular machinery of the nucleus that reads and translates the genome.

"This provides a very simple explanation for how cells prevent access to genes," said Geeta Narlikar, PhD, professor of biochemistry and biophysics and senior author of the study.

'Bad News' Led to New Discovery

Narlikar's graduate student Adam Larson was trying to purify HP1α, and noticed that the liquid in his samples was growing cloudy. For protein scientists, this is typically bad news, said Narlikar: it suggests that proteins that should dissolve in water are instead clumping together into

a useless mass.

But Larson thought the clumps might actually be useful. After all, previous work had shown that the role of HP1α is to sequester long strands of DNA into very small volumes. What if this was exactly the sort of clumping he was seeing in the tube?

Larson took his samples to the lab across the hall from Narlikar's, where Roger Cooke, PhD, professor emeritus of biochemistry and biophysics, helped him examine under the microscope what could have been just a tangled molecular mess. Instead, Larson and Cooke saw clouds of delicate droplets floating around in the water, like a freshly shaken mix of oil and vinegar.

HP1α had a reputation as a difficult protein to work with – get any solution too concentrated, and the protein would clump out. But if the protein was supposed to clump, said Narlikar, "a lot of things we couldn't explain started to make sense."

Narlikar speculates that other scientists may have seen the same cloudiness before, but thinking it was simply a ruined sample, never pursued it like Larson did. "It demonstrates the power of curiosity-driven research," she said.

Rapidly Compacting DNA

To see how and why the HP1α formed droplets, the team produced different mutant versions of the protein, watching which separated out. By watching which parts of the protein were important for forming droplets, and using X-rays to monitor changes in the protein's shape, the team found that the protein nearly doubles in length when small phosphate residues are added in cetain locations. "The molecule literally opens up," said Narlikar. "I was surprised at the size of the change."

This opening-up exposes electrically charged regions of the protein, which stick together, turning dissolved pairs of proteins into long chains that clump together into droplets. Just as balsamic vinegar's dark and flavorful molecules don't seep into the oil of a salad dressing without some extra effort by the chef, the molecules for reading DNA don't seep into the HP1α droplets.

The fact that such a drastic change in shape comes from such a small modification may allow the cell to tightly regulate where and when HP1α silences genes, said Narlikar. The changes come quickly and robustly too – using a technology employed by Sy Redding, PhD a Sandler Fellow, the team created a "curtain" of DNA molecules pulled straight by fluid flowing around them, then added HP1α and watched the protein compress the DNA into tiny droplets, folding it up against the flow.

"People have been seeing for over a hundred years that you get these dense regions of DNA in the nucleus," said Madeline Keenen, the Ph.D. student who ran the curtain experiment. "Now we're seeing the actual mechanism."

More information: Adam G. Larson et al. Liquid droplet formation by HP1α suggests a role for phase separation in heterochromatin, *Nature* (2017). DOI: 10.1038/nature22822

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