

Navigating the Nucleosome

Uncovering genomic instructions for how DNA is packaged reveals a new dimension of the genetic code.

The eukaryotic genome can be up to 130 billion base pairs long, but required to fit inside each cell nucleus. To do this, DNA is tightly wrapped around histone proteins in bead-like clusters. Each cluster is called a nucleosome. For years, mapping experiments had revealed that nucleosomes favored particular DNA sequences, reflecting the ability of certain DNA sequences to bend more sharply and wrap around histones. Still, whether such preferences actually meant DNA coded for the positions of nucleosomes in vivo was unclear.

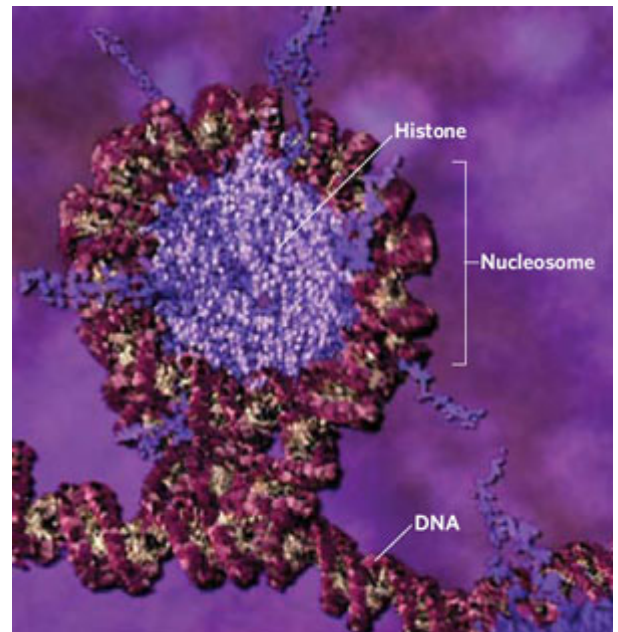
Then, in 2006, Eran Segal at the Weizmann Institute of Science, and Jonathan Widom at Northwestern University, and their colleagues, revealed they could predict nucleosome position based on DNA sequence alone with roughly 50% accuracy—significantly better than the 35% predicted by chance.¹ To do so, they first mapped out and compared DNA sequences that were incorporated into about 200 yeast nucleosomes to figure out what sequences nucleosomes in general might prefer. They next devised computational methods to analyze the probability of a nucleosome occurring at any base pair in a genome based off those preferences, and calculated predictions of where nucleosomes might occur. The study, this month's Hot Paper, revealed what seems to be another code in DNA that helps control where nucleosomes are positioned, and depends on the particular chromosome. Since nucleosomes regulate what transcription factors and other molecules can access and bind to DNA, this means genomes not only encode the instructions for life but can also regulate how they are read out.

"It really brought together a number of disparate observations made in the past decade or two and synthesized them into a clear global model for how things might work," says Jason Lieb at the University of North Carolina. The model the Hot Paper proposed proved "provocative," he adds, and helped trigger a wave of new research.

More mapping

Nucleosome mapping efforts have been revolutionized several times over in the space of just two years thanks to breakthroughs in DNA sequencing technology, Widom says. High-resolution tiling microarray studies have yielded millions of measurements of where nucleosomes tend to appear across the genome.² Parallel DNA sequencing studies have produced hundreds of thousands of full-length nucleosome DNA sequences. "Whereas our paper was based on a detailed analysis of roughly 200 carefully isolated and conventionally sequenced nucleosomes," Widom says, "there are now greater than 500 million experimentally mapped nucleosomes between different organisms, that's an increase of two-million-fold relative to where we were."

Such advances in mapping nucleosomes lead to improvements in predicting nucleosome position based on DNA sequence, Widom says. "We can now predict regions that are more nucleosome dense or less dense than average



DNA (magenta) wraps around histones (violet) to form pearl-like nucleosomes, which wind up to form chromatin fibers. [Click here to watch an animation of DNA packaging.](#)

Animation by Drew Berry. Used with permission from the Howard Hughes Medical Institute, © 2002.

89% of the time across the entire genome, and 98% of the time in especially high-occupancy nucleosome regions," according to findings currently in press.

A number of experiments inspired by the 2006 paper are now underway to test how well DNA sequences code for nucleosome positions, Lieb says. "The problem with an in vivo study of nucleosome positioning, like you had with Segal and his colleagues' paper, is that there are all these transcription binding factors and enzymes there in the nucleus that could move nucleosomes around, so it's hard to separate out the influence that DNA sequences play," he explains. "The next round of experiments will take an in vitro approach using actual genomic DNA to see where nucleosomes like to bind in the absence of any other factors." Widom notes his group and others are hard at work on such experiments, although no one has published any results yet.

Not everyone is convinced DNA sequences play a huge role in nucleosome position. Results from Frank Pugh's lab at Pennsylvania State University suggest that nucleosome positioning "just has to do with packing," says Pugh.³ "If you pack tennis balls in a tube that is capped, the tennis balls can only move so many places. We think the same is happening for nucleosomes as well."

The bigger picture

Will nucleosome findings in yeast hold true for other organisms, including humans? Recent nucleosome mapping experiments in *Caenorhabditis elegans* conducted by Andrew Fire at Stanford University suggest that sequence-directed nucleosome positioning may play a less prominent role in multicellular eukaryotes.⁴ Still, Widom notes those results may have been skewed because they looked at many cell types all pooled together rather than examined individually—different cell types can each have different nucleosomes, which can muddle interpretation of where nucleosomes are actually positioned throughout an organism.

The biggest remaining question might be what role the nucleosome code has played in evolution. "DNA has evolved not just to code the information that will go on to be translated into proteins [or] read by regulatory proteins, but on top of all that, it has to code how it should be packaged. So what kind of constraint has this placed on way DNA can change over time in eukaryotes?" Lieb asks.

To explore the nucleosome code's impact on evolution researchers are exploring how well nucleosome positioning sequences are preserved within and between species. For instance, Naama Barkai at the Weizmann Institute of Science and her colleagues found last year that DNA rigidity is conserved across yeast species at certain promoters.⁵ Rigid DNA could prevent nucleosomes from forming at those sites, and thus may have evolved and been conserved to prevent nucleosomes from affecting transcription.

"It will be very interesting to see how genomes evolved to deal with the constraints that nucleosomes can impose," Widom says.

Data derived from the Science Watch/Hot Papers database and the Web of Science (Thomson ISI) show that Hot Papers are cited 50 to 100 times more often than the average paper of the same type and age.

E. Segal et al., "A genomic code for nucleosome positioning." *Nature*, 442:772-8, 2006. (Cited in 173 papers)

References

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