

In Potentially Important Discovery, Scientists Find Two Forms Of Genetic Material Chromatin

CHAPEL HILL -- Biologists have discovered what appear to be fundamental differences in the physical properties of the genetic material known as chromatin. Chromatin packages DNA into cells, and the difference was found between chromatin that packages genes and the chromatin that packages DNA with regulatory or unknown functions. The difference represents a previously unrecognized level of genomic organization and complexity, the scientists report, one that may exist in all cells with nuclei. Made in yeast, the discovery offers broad potential uses, said Dr. Jason D. Lieb, a University of North Carolina at Chapel Hill biologist and one of the report authors. "For example, in pathology laboratories, differences in chromatin shape and structure in mammalian cells are routinely determined by staining tissues and observing them under a microscope," said Lieb, also a Carolina Center for the Genome Sciences researcher. "This is an important assay used to identify specific cell types and malignancies. It is possible that a detailed genomic view of these variations, provided by the method we describe in our paper, could be used to diagnose and sub-type cancer and other diseases." It also could be an important tool for assigning functions to subsections of the genome, particularly for finding active genes, which remains a difficult problem, he said. The report appears in the May 27 issue of the Proceedings of the National Academy of Sciences. Other authors, all at Stanford University, are Drs. Peter L. Nagy and Michael L. Cleary of the Department of Pathology and Dr. Patrick O. Brown of the Department of Biochemistry.

"If the DNA from a single human chromosome were stretched and measured end-to-end, it would extend to over half an inch in length," Lieb said. "Our cells are much, much smaller than that, of course, and in order to fit inside the cell's nucleus, which is even smaller, DNA must be compacted about 1,000-fold relative to its stretched-out length. This compaction is achieved by coiling and folding the DNA around proteins."

Together, he said, DNA and proteins are called chromatin, and it is chromatin that one sees in the familiar microscopic images of chromosomes. The basic unit of chromatin is called the nucleosome, which is like a barrel, and DNA is wrapped around that barrel 1.7 times. Nucleosomes are made up of proteins called histones, which come in many different "flavors."

"They can be modified by chemical processes known as methylation, acetylation and phosphorylation at different positions," Lieb said. "It has become increasingly clear that specific combinations of histone modifications are linked to underlying gene activity."

Based on its emerging importance, the information stored in histones and their modifications has been dubbed the "histone code," he said. Packaging DNA serves not only to compact it but also has a key role in determining whether the genes are turned on or off, the scientist said. Packaging DNA into chromatin acts as a gatekeeper, determining which parts of the genome are accessible to regulatory proteins and which parts are off-limits. Defects in the proteins that organize DNA are known to lead to embryonic development defects due to their influence on underlying gene activity. That

the DNA sequence in the genome is organized into two broad classes, genes and non-genes (sometimes called "junk DNA") has been known for a long time, Lieb said. Much less is known about how chromatin is organized along the underlying DNA.

"We initially set out to investigate the global distribution of a particular flavor of one histone in yeast," he said. "In the procedure, we crosslinked, or fixed, the yeast with formaldehyde, and then later were to reverse those crosslinks with heat. We inadvertently omitted the reversal, a key step in the technique, however. We found then that by using formaldehyde-crosslinked chromatin in a biochemical procedure normally used to separate all proteins from all DNA, we could instead separate yeast chromatin into two specific and functionally distinct parts."

The most striking aspect of the result, he said, is that local variation in chromatin composition and structure is known to be extremely diverse and complex, yet the new studies reveal what appears to be a global pattern that systematically and simply demarcates sequences in a way that reflects their assigned role as genes or non-genes.

"This method, or a similar method, may be applicable to other organisms," Lieb said "Our approach has potential use as a tool for describing changes in chromatin structure that accompany different genetic, environmental, and disease states."

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