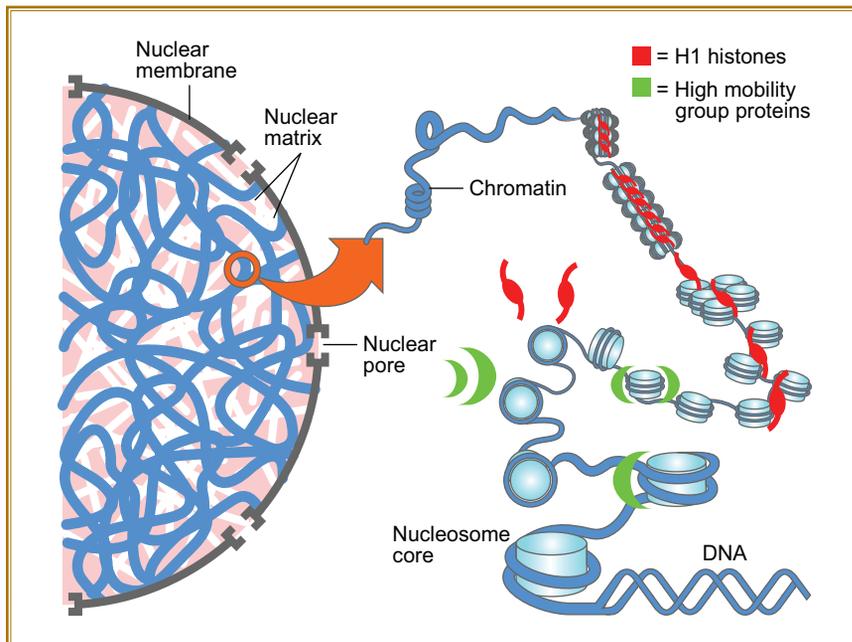


# CECB: Capturing Dynamic Changes in Chromatin



Deoxyribonucleic acid (DNA) contains the instructions a cell uses to build proteins essential to life. The complete supply of DNA is packaged inside the cell as macromolecules called chromosomes; the complete set of chromosomes is called a genome. Each chromosome houses many working units called genes, and each gene sits within tightly coiled DNA strands that are wrapped around eight histone proteins in a package called a nucleosome. Chromatin is the full collection of these nucleosomes. The genome is stored in the cell nucleus.

Trends in research sometimes veer away from the path of important discoveries, and the study of chromatin's architecture is a good example of this. Until recently, scientists were not convinced that nucleosomes or histones interact dynamically with DNA. DNA topology was viewed statically, as if its primary sequences alone determined its actions. Many scientists dismissed the idea that DNA topology plays a regulatory role in chromosome biology.

Today scientific perceptions of chromatin have shifted radically from this static view to a dynamic model, in part, because of the outstanding research conducted by NCI's Center of Excellence in Chromosome Biology (CECB), one of five Centers of

Excellence within NCI's Intramural Research Program. CCR Director Robert Wiltrot, Ph.D., created the collaborative infrastructure in 2006 to unite diverse research skills and to investigate the multiple factors that enable dynamic changes to occur in DNA topology. Currently, over 40 NCI investigators are members or serve on a steering committee, chaired by Gordon Hager, Ph.D., Chief of CCR's Laboratory of Receptor Biology and Gene Expression, that guides CECB activities.

Working through the Center, CCR scientists peer into the nucleus and study how cells regulate rapid responses to physiological stimuli in real time. With this new approach, CECB scientists have redefined chromatin's role in the cell.

"Chromatin and chromosome biology is only in its infancy," explains Hager, "yet epigenetics has already become central to a mechanistic understanding of nuclear function."

CECB investigators have shown that DNA topology changes frequently and that those changes have consequences. They have redefined the operational mechanisms by which proteins and DNA interact during replication, RNA transcription, and DNA repair.

The CECB's success continues as its members share their prolific findings with colleagues across the NIH campus and with the extramural community. The *NCI Symposium on Chromosome Biology*, hosted every 18 months by CECB, has grown into an international conference. The most recent symposium, "Epigenetics in Development," was held in April on the NIH campus in Bethesda, Md., and attracted about 700 attendees from around the world.

The CECB also hosts a quarterly trans-NIH workshop with the NIH Chromatin Interest Group. The goal of this workshop is to cultivate interactions among major laboratories in chromosome biology, and to enhance the education and development of junior investigators and fellows in CECB laboratories. Postdoctoral fellows working in chromosome biology have also created and sponsor their own seminar series, called Chromatin Decode. This series provides a more informal forum for postdoctoral fellows to present their ongoing work.

The increasing interest in CECB, which extends beyond NIH, can be largely attributed to the singular



## Center of Excellence in CHROMOSOME BIOLOGY

discoveries made by its members. Early in the Center's young life, CECB member Tom Misteli, Ph.D., reported insightful results after visualizing a set of mouse chromosomes and analyzing their positions in the 3D space of the cell's nucleus. Later he and his team did similar work in human cancer cells. Their evidence pointed to the possibility that the arrangements and spatial relationships among chromosomes are far from random. Misteli and his research team demonstrated further that chromosomes actually cluster into distinct topological neighborhoods, and that the resulting positional patterns differ depending on cell type. They discovered that these patterns are not just passive bystanders in genome function. Quite the contrary, they play a key role in chromosome rearrangements. Using cancer cells, the Misteli team showed that proximity, in part, dictates the nature of genomic rearrangements.

Working in this same area of research, the Misteli lab recently also reported that broken chromosomes—that do not reanneal—are unable to undergo dynamic motion within the nucleus. This surprising result is now thought to be an important cancer suppressing mechanism.

Chromosome biology researchers also tackle another area of dynamic chromatin, namely, the dynamic binding of transcription factors, using steroid receptor proteins as an example. Hager and colleagues discovered that a large fraction of genomic receptor binding requires a localized open conformation of the chromatin prior to hormone signaling. They demonstrated that cell-specific proteins determine

tissue selective hormone-driven transcription by opening chromatin at subsets of all genomic receptor binding elements. For mammary cells, a constitutive nuclear protein called AP1 maintains chromatin in an open state at these elements, keeping them ready for action. Importantly, the CCR scientists showed that baseline chromatin accessibility is actively maintained by constitutive AP1 binding, keeping it ready for more specific actions. It directs traffic as inducible transcription factors arrive in response to hormone signaling.

CECB member Mirit Aladjem, Ph.D., realized that a proper start of DNA replication may require proteins that bridge distant chromosomal sequences together. This fact did not intimidate Aladjem from tackling the mechanisms involved and from publishing the first comprehensive mapping of the locations of all replication starting points in several cancer genomes. She realizes that unraveling the chromatin dynamics during replication will be very important for understanding the regulation of cell growth, and that sequences that affect replication might improve the future design of effective gene therapy vectors. (See "It Starts with a Choice," page 22.)

In addition to studying topology, CECB scientists also look carefully at post-translational modifications to chromatin, an area of research called epigenetics. While studying the role of epigenetics in altering chromosomal architecture, CECB member Charles Vinson, Ph.D., showed how methylation of CpG sites within chromatin

actually recruits sequence-specific transcription factors that are essential for some tissue-specific gene expression.

Aware that DNA in B cells routinely breaks and recombines genetic information to build proteins with specific antibody shapes, CECB member Andre Nussenzweig, Ph.D., realized that this function in itself could increase chromosomal translocations in B cell lymphomas. So he and his research team pursued the abnormal chromatin interactions that occur in B cell lymphoma and discovered how normal B cells protect themselves against accumulating the excessive DNA breaks that can lead to unwanted translocations.

These and similar discoveries keep coming from the laboratories of CECB members. The Center's prolific work in support of the importance of chromatin's dynamic architecture has resulted in a special issue of the journal *Biochimica et Biophysica Acta (BBA) Gene Regulatory Mechanisms* entitled "Chromatin in time and space." Elsevier released the print version, containing 31 articles authored by CECB and NIH chromatin group scientists, in July 2012.

Paying attention to chromosomal topology is a new trend that has changed the field of chromosome biology. By characterizing chromatin's three-dimensional organization and dynamics, members of CCR's CECB are enlightening the scientific community about how chromatin's topology exerts regulation on gene activities and how chromatin aberrations lead to disease.

*To learn more about the Center of Excellence in Chromosome Biology, please visit its Web site at <http://chromosomebiology.nci.nih.gov>.*