Researchers identify another piece of the 'histone code' puzzle

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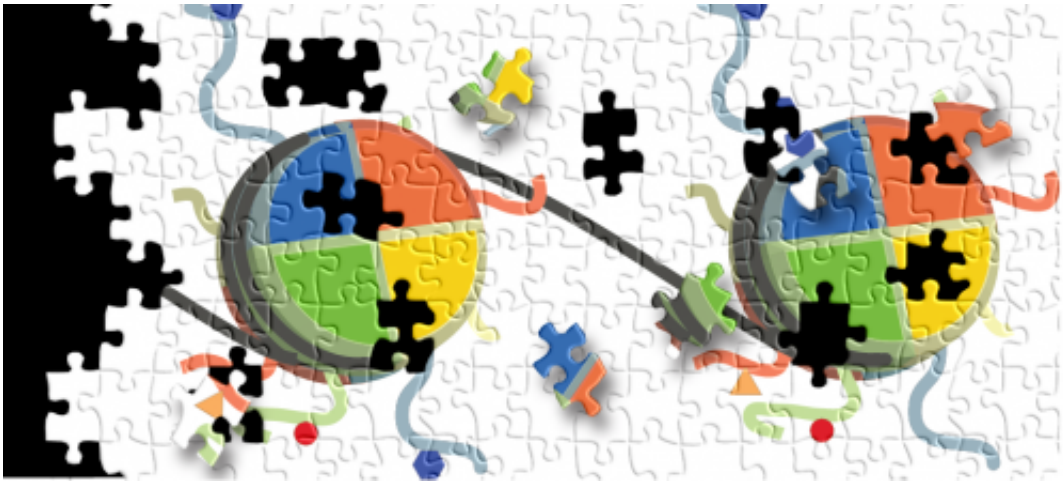

Research in the Strahl lab helps to piece together how the 'histone code' contributes to chromatin regulation. Credit: Scott Rothbart, PhD

(Medical Xpress)—DNA is often called the blueprint of life, but the four-letter combinations that make up the genetic code are just part of the story. Built upon the DNA lies additional epigenetic information in the form of a complex ensemble of chemical tags attached to the DNA itself and on proteins that package our DNA – called histones – which ultimately control how our genetic code is accessed and used. Interestingly, histones are decorated with many types of chemical tags, and their particular combinations have been referred to as the "histone code." But understanding how the cell interprets the code has proven challenging due to its sheer complexity and a lack of tools to study the

code inside the cell.

Now research from the University of North Carolina School of Medicine has shown how a protein called UHRF1 "reads" the histone code in a specific way to perform an important cellular function. "Because the protein has been found to be defective in cancer, the finding not only lends new insight into functions downstream of the histone code but could also point the way toward novel strategies for cancer treatment and prevention," said senior study author Brian Strahl, PhD, associate professor of biochemistry and biophysics and member of the UNC Lineberger Comprehensive Cancer Center.

The research, which appears June 1, 2013, in the journal *Genes and Development*, is the latest of many studies to investigate the histone code hypothesized more than ten years ago by Strahl and his former postdoctoral advisor C. David Allis. The hypothesis suggests that distinct combinations of histone modifications work together to form a code, akin to the classic genetic code, in which three-letter combinations of nucleotides make an amino acid. These histone modifications – chemical changes like phosphorylation, acetylation and methylation – generate an epigenetic language that is interpreted through the ability to recruit proteins to DNA and histones that in turn modulate cellular functions.

"This study provides important support for the histone code hypothesis, and also reiterates how difficult it will be to crack this code," said Strahl. "It is not enough to understand how one tag works in isolation—we now have to look at all different combinations of tags on both histones and DNA to piece together the puzzle encrypting this second layer of information."

Over the last decade, researchers have pinpointed a number of different "domains" that proteins use to interact with, or read, the histone code. Scott Rothbart, PhD, lead author and a postdoctoral research fellow in

Strahl's laboratory, previously showed that one such domain on the protein UHFR1—the tandem Tudor—helps it bind to a histone in the cell that is methylated at a specific place. Adjacent to the Tudor was another domain called a PHD finger that helped the protein also bind the unmodified end of a histone. Rothbart and Strahl wondered if these neighboring domains might function together to help UHRF1 to read the histone code and, subsequently, influence its ability to function in the cell.

To investigate this question, the researchers used a highly sophisticated peptide microarray technology developed in the Strahl lab. Just as DNA microarrays contain sections of DNA sequence spotted on glass slides, these peptide arrays contained sections of modified histone proteins. When the researchers applied the UHRF1 protein to the array, they found it bound the histone differently when it contained the linked Tudor and PHD domains than when it contained the domains in isolation. They then used biochemical techniques to show that the two domains of UHRF1 functioned together in cells—whereby each domain is making a key contribution to promote binding to the histone protein in a specific way.

One of the main functions of UHRF1 is the maintenance of a critical modification known as DNA methylation. The researchers showed that when these domains of UHRF1 were not functioning together to read the histone code, DNA methylation patterns in the cell were eventually lost.

"Abnormalities in the patterning of DNA methylation are a hallmark of many cancers," said Rothbart. "In addition, UHRF1 has been found to be defective in a number of cancers including prostate, breast, kidney, and lung cancer. UHRF1's function in maintaining DNA methylation seems to be reversible—if you take it out of the cell, you lose DNA methylation, but if you add it back, you restore DNA methylation. We therefore think that by using small molecules to disrupt the recognition

of the histone code by UHRF1, we may be able to reprogram DNA methylation patterns in cancer cells."

Provided by University of North Carolina at Chapel Hill School of Medicine