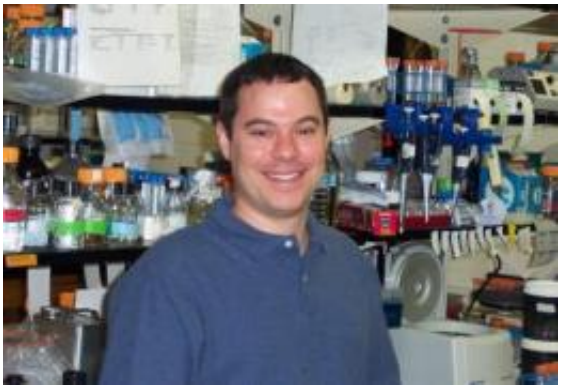
Tools used to decipher 'histone code' may be faulty

December 16 2010



This is Brian Strahl, PhD, of the University of North Carolina at Chapel Hill. Credit: UNC Medical Center News Office

The function of histones -- the proteins that enable yards of DNA to be crammed into a single cell -- depends on a number of chemical tags adorning their exterior. This sophisticated chemical syntax for packaging DNA into tight little coils or unraveling it again -- called the "histone code" -- is the latest frontier for researchers bent on understanding how genetics encodes life.

But recent research from the University of North Carolina at Chapel Hill has found a number of issues with histone antibodies, the main tools used to decipher this code, suggesting they may need more rigorous testing.

"When I have presented our findings at major meetings, the reactions of my peers have been shock and awe across the board," said senior study author Brian Strahl, PhD, associate professor of biochemistry and biophysics at UNC.

"Hundreds and hundreds of researchers around the world use them and assume they are accurate. Yet we have found that they need to be used with caution." Strahl is a member of the UNC Lineberger Comprehensive Cancer Center.

The results of the study, which appears online December 16, 2010, in the journal Current Biology, also found that the proteins that interpret the histone instructions are affected not just by the specific chemical tag they land on but also by other tags in the neighborhood.

The "Histone Code" was first proposed almost ten years ago by Strahl and epigenetics researcher C. David Allis, who was his postdoctoral advisor at the time. In a review article published in the journal Nature that has since been cited over 3000 times, Strahl and Allis suggested a model of how histones and their posttranslational modifications may function in chromatin.

Histones are the protein spools around which strands of DNA are wrapped to form a package called chromatin. Depending on the modifications or tags decorating the histones, DNA is either closed up tightly within this package or lies open so that its genes can be read.

Strahl and Allis hypothesized that distinct combinations of histone modifications work together to form a code, akin to the classic genetic code in which distinct combinations of nucleotides make an amino acid. These histone modifications – chemical changes like phosphorylation, acetylation and methylation -- generate a language that is interpreted through the ability to recruit the proteins that modulate chromatin.

"But this histone code is way more complicated, because there are over a 100 different histone modifications, and they are working in a three-dimensional space that is very difficult to visualize," said Strahl. "We can't say that this mark or this combination of modifications will always mean a certain thing. But what I think we can say is that multiple modifications can help tip the balance of one chromatin state to another, making the underlying DNA more or less accessible to the protein machinery."

In order to uncover what some of those codes might be, the researchers started generating chunks of histone proteins, each engineered to contain various combinations of modifications. In a completely new approach to the histone code, Strahl and his colleagues printed these modified chunks or peptides onto glass slides, generating peptide arrays akin to DNA arrays.

When they tested widely used commercial antibodies that were directed against specific modifications on histones, like methylysine or methylarginine, they found the antibodies didn't always recognize the site they were supposed to, sometimes even binding to off-targets better than their intended target.

The results fit nicely with a study published recently in Nature Structural Biology by Jason Lieb, Ph.D., a professor of biology at UNC and a Lineberger Center member. Lieb used older approaches like immunofluorescence, CHIP and Western blots to show that many commercial antibodies were not performing as they should.

An additional finding of the study by Strahl and colleagues was that antibodies, as well as the proteins that naturally bind chromatin, were greatly affected by neighboring modifications.

"This result gives further support to the idea of the histone code, in that

the ability of a protein to bind to histones may depend on a particular modification landscape and not just one single modification" said Strahl. "The presence of an acetylation site nearby could impact the binding of a protein at its intended phosphorylation site. So altogether these modifications generate a landscape that is vitally important in how proteins read the histone code."

Provided by University of North Carolina School of Medicine

Citation: Tools used to decipher 'histone code' may be faulty (2010, December 16) retrieved 20 April 2024 from https://phys.org/news/2010-12-tools-decipher-histone-code-faulty.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.