Team decodes another piece of the histone code puzzle

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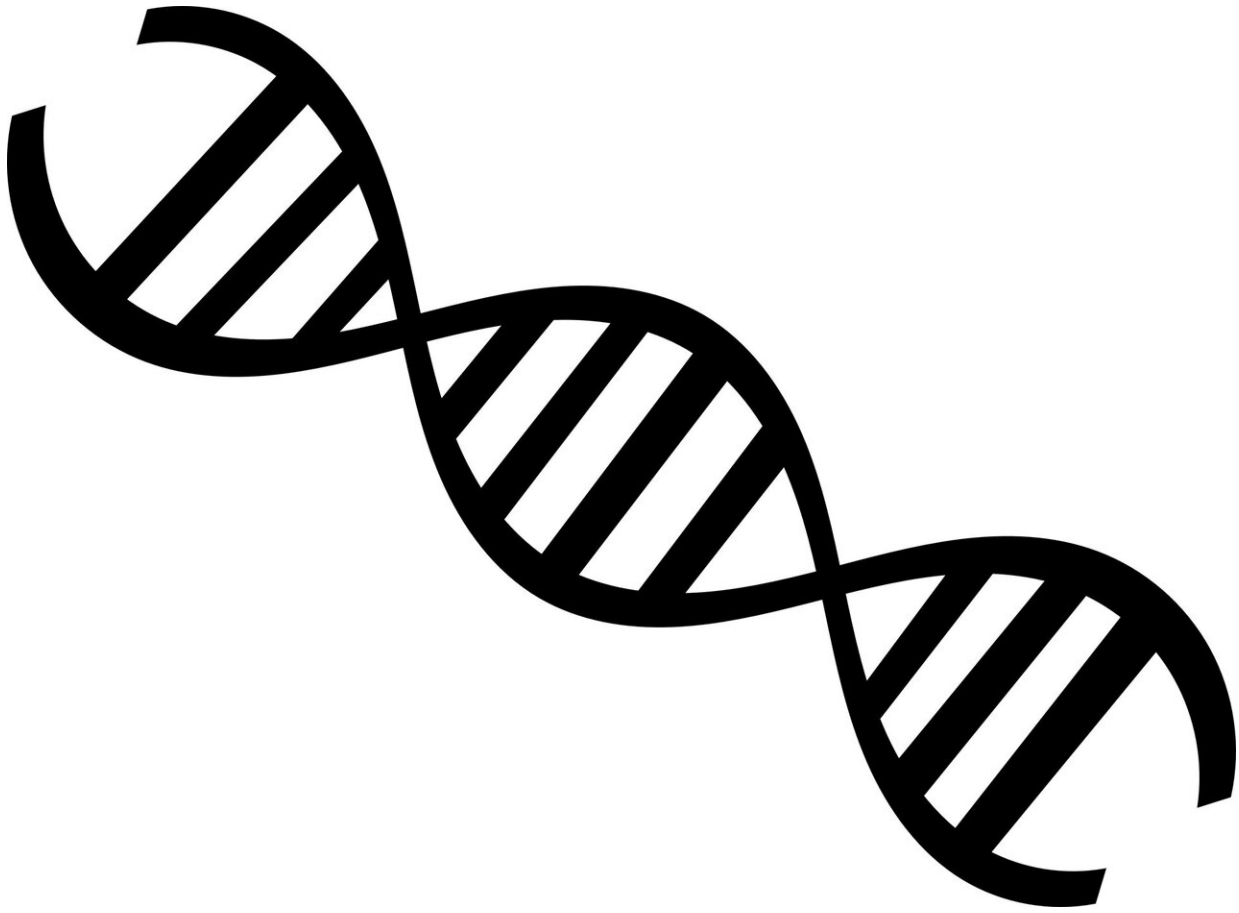

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Inside our cells, DNA is tightly packed and spooled around proteins called histones. Packaging DNA in this way allows large amounts of

genetic material to exist inside the cell in a final form called chromatin. Tiny enzymes modify the histones to make sure the genes that are part of the DNA can be accessed and precisely regulated. The result of this is proper gene expression and the production of proteins important for cell function and human health. When this process goes awry, the result can be diseases such as cancers.

The lab of Brian Strahl, Ph.D., interim chair of the UNC Department of Biochemistry and Biophysics, has been studying this process for years and has now revealed another piece of an intricate epigenetic puzzle—how one enzyme can lead to slightly different chemical modifications that control distinct biological functions important for gene expression and the repair of DNA.

Published in the journal *Cell Reports*, this research reinforces the notion that the multiple chemical modifications placed on histones by a single enzyme ensures multiple and distinct functions—an idea that was postulated by Strahl and his former mentor, David Allis, Ph.D., and was called the Histone Code hypothesis.

The Histone Code is important for genome function, yet the rules that govern the code are not fully deciphered. One of the early findings in the field of epigenetics was that a class of enzymes called histone methyltransferases can add a chemical modification multiple times on a single amino acid residue of a histone.

The process by which a histone methyltransferase adds this chemical modification is called methylation. The methyltransferase adds one carbon atom and three hydrogen atoms—a so-called 'methyl group' to a specific amino acid reside of a histone. This process can occur once, twice, or three times on a single amino acid residue, creating different "flavors" of methylation.

A major question in the field had been: do different "flavors" of methylation have the same or distinct biological functions on, say, gene expression important for the maintenance of healthy cells? While other studies had explored this idea for some histone sites that are methylated, many locations of histone methylation had not been investigated.

To answer this question, first author Julia DiFiore, Ph.D., a graduate student in the Strahl lab at the time of this research, genetically engineered one such methyltransferase called Set2 so it could perform only select flavors of methylation on its amino acid within histones. By achieving this high degree of specificity, the researchers could finally test if the different degrees of methylation at this site have the same or distinct functions.

"We found there are indeed unique functions, as well as shared functions, in gene expression and in DNA repair," Strahl said. "Our findings help to uncover the potential for different methylation states on histones to regulate diverse chromatin functions."

In addition to understanding fundamental cellular processes, "This work could also explain how dysregulation of enzymes such as Set2 might lead to incorrect 'flavors' of methylation to cause human disease," said Strahl, an Oliver Smithies Investigator at the UNC School of Medicine and member of the UNC Lineberger Cancer Center.

One process they examined was how stress conditions—specifically nutrient stress—affects gene expression. Strahl's group observed that when no methylation on the histone H3K36 was present, gene expression was very different than when normal amounts of methylation were present during nutrient stress. Interestingly, they observed that having only two or only three methyl groups (also called di- and trimethylation) had exactly the same effect as having all three types of methylation that are normally present.

DiFiore explained, "During nutrient stress, the overlapping roles of di- and trimethylation help provide flexibility to dynamic processes and better allow the cell to respond to stress." Being able to quickly respond to stress allows the cells to grow and function properly even under less than ideal conditions.

In future studies, Strahl's lab will examine the functions of the different forms of this methylation event in other important cellular contexts and in other model systems including human cells. They hope to put their findings into a broader context of how histone methylation functions and if the inappropriate changes found with these methylation events in human diseases, such as cancers, are behind how these diseases are formed.

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