Scientists take a step towards uncovering the histone code

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Researchers at Emory University School of Medicine have determined the structures of two enzymes that customize histones, the spool-like proteins around which DNA coils inside the cell.

The structures provide insight into how DNA's packaging is just as important and intricate as the information in the DNA itself, and how these enzymes are part of a system of inspectors making sure the packaging is in order.

The results are published online this week in the journal Nature Structural and Molecular Biology.

A team of scientists led by Xiaodong Cheng, PhD, professor of biochemistry at Emory and a Georgia Research Alliance eminent scholar, used X-rays to probe the architecture of two enzymes, PHF8 and KIAA1718. The enzymes are known as histone demethylases because they remove methyl groups (chemical modifications of a protein) from histones.

Mutations in the gene encoding one of the enzymes, PHF8, cause a type of inherited mental retardation. Understanding how PHF8 works may help doctors better understand or even prevent mental retardation.

Many biologists believe the modifications on histones are a code, analogous to the genetic code. Depending on the histones' structure, access to DNA in the nucleus can be restricted or relatively free. The

idea is: the modifications tell enzymes that act on DNA valuable information about getting to the DNA itself.

"This work represents a step toward uncovering the molecular basis for how demethylases handle multiple signals on histones," says Paula Flicker, PhD, who oversees cell signaling grants at the National Institutes of Health's National Institute of General Medical Sciences. "Knowledge of how these complex signals help govern patterns of gene activity will bring us closer to understanding how cells determine their identity during development."

To understand histone demethylases' role in the cell, Cheng says, think of the cell as a library with thousands of books in it.

"To find a particular book in a library, you need some signs telling you how the stacks are organized," he says. "Similarly, the machinery that reads DNA needs some guidance to get to the right place."

Histones have a core that the DNA wraps around and flexible tails extending beyond the core. The cells' enzymes attach a variety of bells and whistles - methyl groups are just one -- to the histone tails to remind the cell how to handle the associated DNA.

Methyl groups mean different things depending on where they are on the histone. In addition, the modifications vary from cell to cell. In the brain, for example, the modifications on a particular gene might signal "this gene should be read frequently," and in muscle, a different set of modifications will say "keep quiet."

"What these enzymes do is make sure all the signs are consistent with each other," Cheng says. "If a sign is out of place, they remove it."

PHF8 and KIAA1718 are each made up of two attached modules. One

module (called PHD) grabs a histone tail with a methyl group on it, while the other module (Jumonji) removes a methyl group from somewhere else on the tail.

Scientists previously knew the structures of the methyl-binding and methyl-removing modules in isolation. What is new is seeing how the modules are connected and how one part regulates the other, Cheng says.

More information: Enzymatic and Structural Insights for Substrate Specificity of a family of Jumonji Histone Lysine Demethylases. J.R. Horton, A.K. Upadhyay, H.H. Qi, X. Zhang, Y. Shi and X. Cheng. Nature Struct. Mol. Bio. 17 (2009).

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