# Scientists find missing link between players in the epigenetic code

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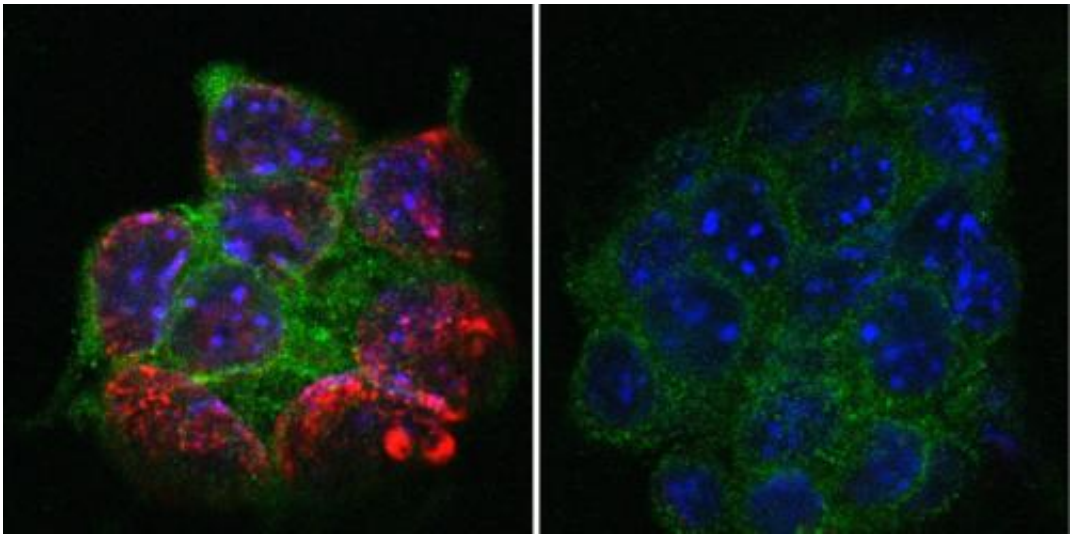

Mouse embryonic stem cells (blue, green) lose DNA methylation (red) in the absence of UHRF1. Credit: Strahl Lab, UNC School of Medicine

Over the last two decades, scientists have come to understand that the genetic code held within DNA represents only part of the blueprint of life. The rest comes from specific patterns of chemical tags that overlay the DNA structure, determining how tightly the DNA is packaged and how accessible certain genes are to be switched on or off.

As researchers have uncovered more and more of these "epigenetic" tags, they have begun to wonder how they are all connected. Now, research from the University of North Carolina School of Medicine has

established the first link between the two most fundamental epigenetic tags—histone modification and DNA methylation—in humans.

The study, which was published Sept. 30, 2012 by the journal *Nature Structural & Molecular Biology*, implicates a protein called UHRF1 in the maintenance of these epigenetic tags. Because the protein has been found to be defective in cancer, the finding could help scientists understand not only how microscopic chemical changes can ultimately affect the epigenetic landscape but also give clues to the underlying causes of disease and cancer.

"There's always been the suspicion that regions marked by DNA methylation might be connected to other epigenetic tags like histone modifications, and that has even been shown to be true in model organisms like fungus and plants," said senior study author Brian Strahl, PhD, associate professor of biochemistry and biophysics in the UNC School of Medicine and a member of UNC Lineberger Comprehensive Cancer Center. "But no one has been able to make that leap in human cells. It's been controversial in terms of whether or not there's really a connection. We have shown there is."

Strahl, along with his postdoctoral fellow Scott Rothbart, honed in on this discovery by using a highly sophisticated technique developed in his lab known as next generation peptide arrays. First the Strahl lab generated specific types of histone modifications and dotted them on tiny glass slides called "arrays." They then used these "arrays" to see how histone modifications affected the docking of different proteins. One protein – UHRF1 – stood out because it bound a specific histone modification (lysine 9 methylation on histone H3) in cases where others could not.

Strahl and his colleagues focused the rest of their experiments on understanding the role of UHRF1 binding to this histone modification.

They found that while other proteins that dock on this epigenetic tag are ejected during a specific phase of the cell cycle, mitosis, UHRF1 sticks around. Importantly, the protein's association with histones throughout the cell cycle appears to be critical to maintaining another epigenetic tag called DNA methylation. The result was surprising because researchers had previously believed that the maintenance of DNA methylation occurred exclusively during a single step of the cell cycle called DNA replication.

"This role of UHRF1 outside of DNA replication is certainly unexpected, but I think it is just another way of making sure we don't lose information about our epigenetic landscape," said Strahl.

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