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The whole of epigenetic regulation may be greater than the sum of its parts

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Scientists may be closer to answering a long-standing question in biology—how do the components of cells' molecular machinery work together to transmit vital gene regulatory information from one cell generation to the next?

New findings published in *eLife* draw connections between some of these pieces, revealing an extensive web of molecular interactions that may ultimately inform the development of new epigenetic drugs for cancer and other diseases. Specifically, the study reveals a mechanism that helps explain how dividing cells pass patterns of epigenetic information called methyl tags to their daughter cells, a crucial part of regulating gene expression across cell generations.

Epigenetic tags help tell genes—stretches of DNA that act as biological instruction manuals—when to switch "on" and "off," ultimately determining cell type and function. DNA methylation, or the addition of methyl tags to DNA, is one of the most well-studied epigenetic signals; errors in this process are commonly found in cancer.

"Many of the key players orchestrating DNA methylation had previously been characterized, but what we didn't fully realize before this study is that they all work together in an elegant way," said Scott Rothbart, Ph.D., assistant professor at Van Andel Research Institute (VARI) and the study's senior author. "These new insights into the complexities of epigenetic regulation are contributing to our basic understanding of this process in human health and disease and gives us new vision for how to

go about targeting errors in DNA methylation with innovative drug therapies."

The findings center on a protein called UHRF1, a guardian of the cell's epigenetic information that can recognize patterns of epigenetic tags and promote the addition of new ones. These "reading" and "writing" activities of UHRF1 are well understood on their own but until now, scientists didn't know exactly how or even if these UHRF1 activities worked together. Rothbart's team, along with collaborators from University of North Carolina at Chapel Hill, University of Washington and University of Toronto, tackled this problem by asking two questions—how does UHRF1 get to where it needs to be? And once it's there, what does it do?

Here's what they found—during cell division, UHRF1 recognizes newly copied DNA at sites that are missing methyl tags. At the same time, it also recognizes a protein associated with DNA called histone H3 and attaches another small protein called ubiquitin on that histone. This ubiquitin protein acts as a molecular flag, signaling to another protein called a DNA methylation enzyme that a methyl tag is needed there. The group discovered that ubiquitin attachment on the histone is promoted by the pre-existing pattern of epigenetic signals recognized by UHRF1. This is the first time an epigenetic signal has been shown to impact ubiquitylation and connects the patterns of epigenetic information in a new way.

"While the functions of the individual parts of UHRF1 were already known, we didn't appreciate the interdependence of these functions in adding ubiquitin to histones," said Joe Harrison, Ph.D., a postdoctoral fellow in the Kuhlman Laboratory at UNC and the paper's first author. "This exquisite regulation of an ubiquitin ligase has not been previously described and is very exciting for the field of ubiqutin biology."

Drugs that impact DNA methylation are increasingly a target for drug development; in fact, several of these therapies are already in clinical use for certain cancers. With this new knowledge, the next step, Rothbart says, is to develop robust screening methods to find compounds that correct errors in this process.

More information: Joseph S Harrison et al. Hemi-methylated DNA regulates DNA methylation inheritance through allosteric activation of H3 ubiquitylation by UHRF1, *eLife* (2016). DOI: 10.7554/eLife.17101

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