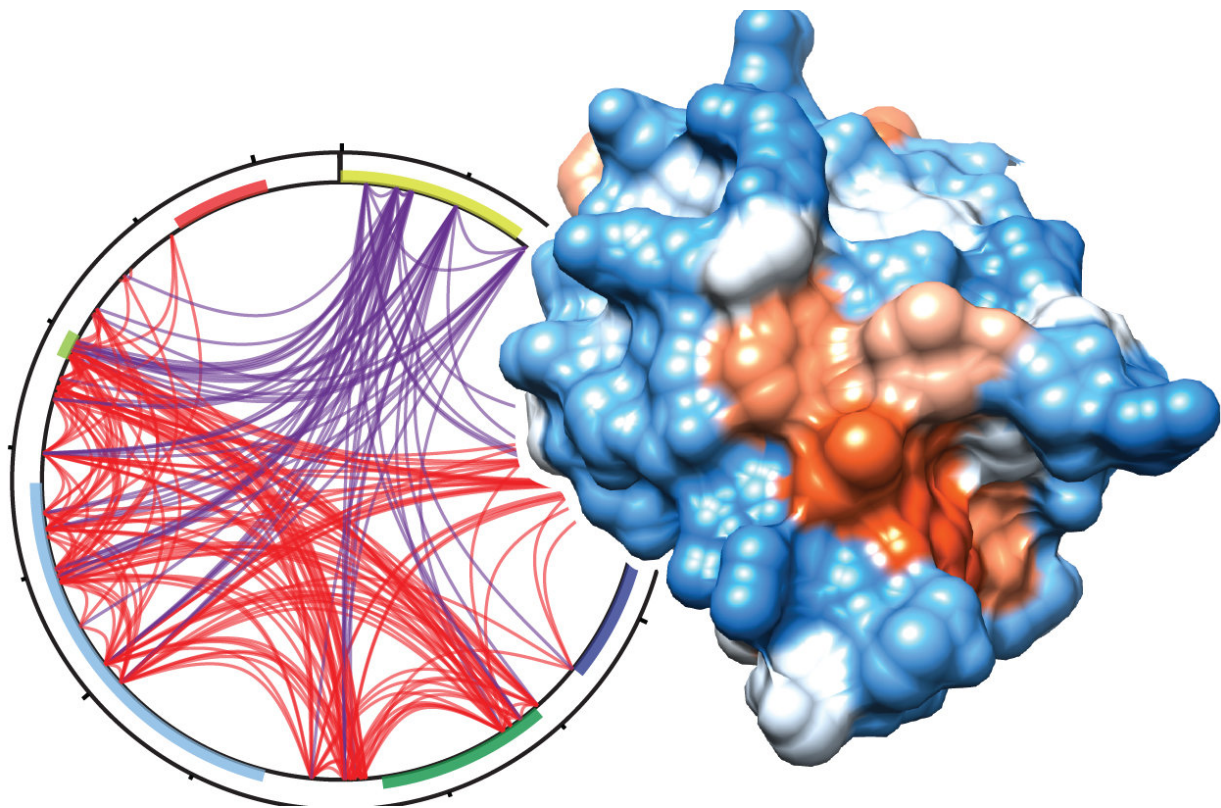


A new piece to the puzzle sheds light on how UHRF1 regulates gene activity

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UHRF1 may serve as a target for drug therapies. Credit: © Helmholtz Zentrum München

Epigenetic changes often play an important role in cancer, because they cause the genetic material to be read incorrectly at certain locations. Genes that are especially critical are those that control the growth and

death of cells. Scientists at Helmholtz Zentrum München have now discovered new details about the UHRF1 protein. UHRF1 catalyses particular steps that are required for marking DNA with epigenetic modifications that suppress parts of the genome. As reported in *Molecular Cell*, the molecule may serve as a target for drug therapies because it is produced at elevated levels in cancer cells.

All cells have the same complement of genes, yet perform entirely different functions. This is because genes are read differently depending on the type of cell in which they occur. Gene activity is regulated not only at the level of the DNA sequence, but also at the epigenetic level by a variety of chemical modifications made to DNA and histones.

"Histones are proteins that 'package' the DNA strands in the nucleus into chromosomes. But they also play an important role in controlling gene expression," says Prof. Dr. Robert Schneider, Director of the Institute of Functional Epigenetics (IFE) at Helmholtz Zentrum München.

Together with other proteins, DNA molecules and histones form chromatin. This constitutes a chemical method for condensing genetic information within the small space of the cell nucleus. Very little is known about these regulatory processes that are the focus of the research at IFE.

UHRF1 controls key steps in DNA methylation

Researchers know, however, that the [protein](#) UHRF1 (ubiquitin-like, containing PHD and RING finger domains) plays an important role in the methylation of DNA strands. Methyl tags are chemical modifications to a DNA molecule that do not alter the genetic code, i.e. the sequence of bases of the DNA. However, they affect the activity of genes encoded in the base sequence. Methylation of DNA molecules usually acts to repress gene transcription.

UHRF1 controls DNA methylation by ensuring that an enzyme that attaches methyl groups to DNA can bind to newly formed chromatin. To accomplish this task, UHRF1 must first bind to newly formed chromatin itself and, in a second step, transfer an ubiquitin molecule (a small protein that alters the properties of other proteins) to a histone protein. To this end, UHRF1 uses various protein domains, regions with special three-dimensional structures and functions in the same molecule.

"It was not previously known exactly how this works," says Dr. Till Bartke, deputy director of the IFE, who supervised the study. Together with his colleague Dr. Benjamin Foster (post-doctoral researcher at the IFE), he has applied various methods in a bid to shed light on this ubiquitin-transfer step, including chemical crosslinking of molecules, mass spectroscopic studies and the use of recombinant chromatin molecules that were modified with methyl groups. "We found that an ubiquitin-like domain (UBL) must be present to transfer ubiquitin [molecules](#)," Bartke says. This is a special structural element involved in rearrangements of UHRF1 after it has bound to chromatin. In collaboration with a research group led by Dr. Sebastian Bultmann at Ludwig-Maximilians University Munich, the researchers were also able to show that the UBL domain is required for the methylation of DNA in cells.

"Our analysis of the enzymatic mechanism of UHRF1 reveals an unexpected function of the UBL domain and defines a new role of this domain in DNA methylation," the scientist explains. Because other groups have found elevated concentrations of UHRF1 in several cancers, including lung and colorectal cancer, the protein, he believes, is well-suited as a target for future therapies.

More information: Benjamin M. Foster et al, Critical Role of the UBL Domain in Stimulating the E3 Ubiquitin Ligase Activity of UHRF1 toward Chromatin, *Molecular Cell* (2018). [DOI](#):

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