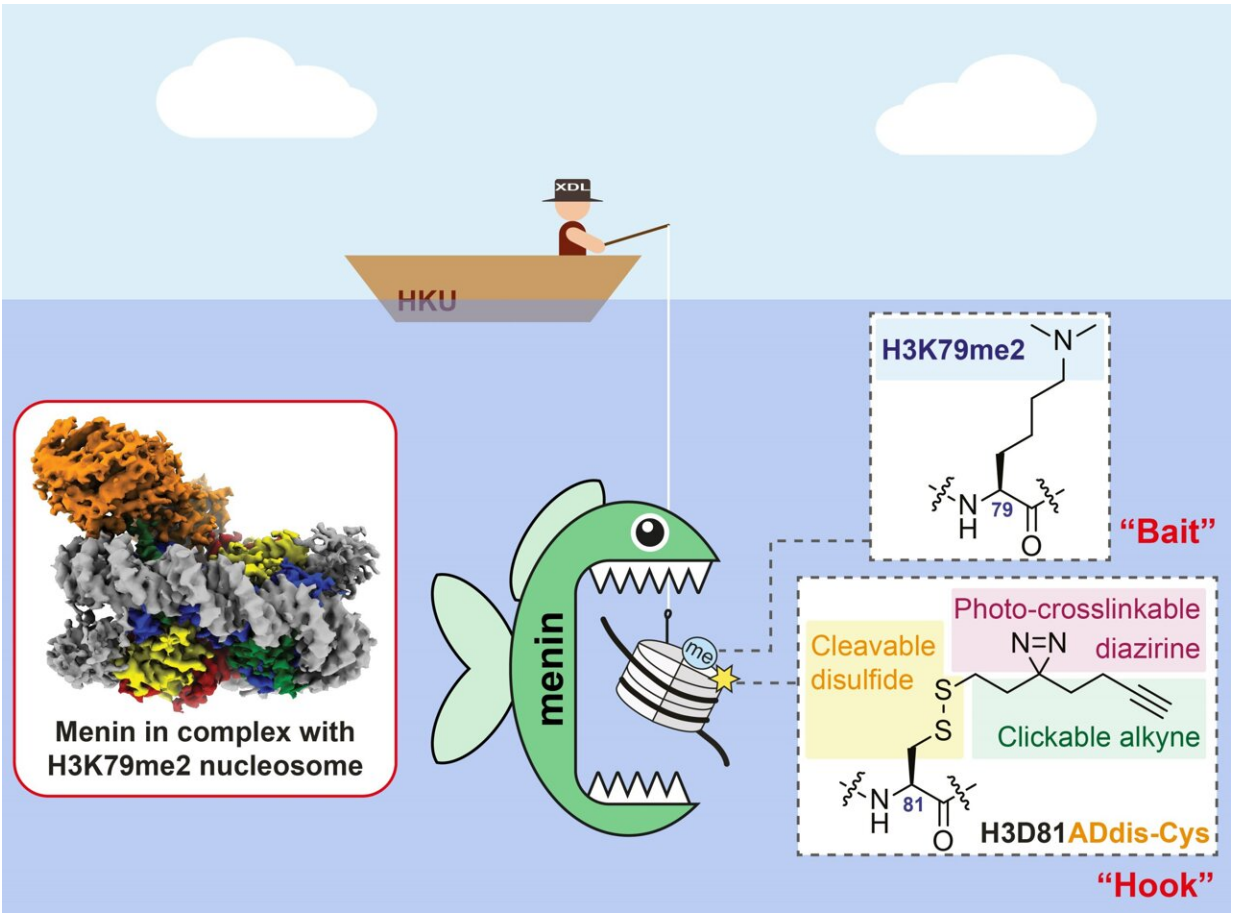
Decoding a histone mark important for a gene regulation that goes awry in cancer

February 17 2023



The research team chemically synthesizes an intact nucleosome with an upgraded tri-functional hook and H3K79me2 as the bait. Using this new technology, the team successfully identified a protein called menin as the reader of H3K79me2. Credit: Xiang David Li Group—The Laboratory of Chemical Epigenetics

A research team from the University of Hong Kong (HKU) led by Professor Xiang David Li from the Department of Chemistry in collaboration with Dr. Yuanliang Zhai from the HKU School of Biological Sciences and Dr. Jason Wing Hon Wong and Dr. Xiucong Bao from the HKU School of Biomedical Sciences recently made a key breakthrough in understanding how genetic information encoded in our DNA is read and why errors in reading such information can often lead to developmental defects or cancers. The findings were recently published in *Science*.

Each type of cell in the human body (with some exceptions) contains exactly the same DNA sequence, known as genes. Therefore, to make a specific cell type (e.g., a stem cell, a neuron), each cell needs to carefully choose which genes to express. This fundamental process is regulated by diverse modifications of histone proteins, which were previously thought of as mere spools for packaging DNA in the nucleus of our cells.

We now know that these histone modifications are tags or marks on chromatin that function as master switches for the regulation of genes—they determine which sets of genes in a cell should be "ON" or "OFF" at the right time and for the right duration. Dysregulation of this fundamental process underlies many severe human diseases such as cancers.

Different types of histone marks act as cellular signals to control various chromatin-associated machineries that regulate gene expression, DNA replication and damage repair. One of the challenges in chromatin biology is how particular histone marks are interpreted to achieve their biological function. To answer this question, it is essential to find the readers, a class of proteins that recognize specific histone marks and translate them by turning the expression of genes up or down accordingly.

However, readers of many histone marks are still unknown, which limits our ability to understand their roles in gene regulation. A long-standing interest of Professor Li's lab is the development of novel chemical approaches to identify histone readers that might be difficult to find using traditional biological methods.

One such method uses a peptide containing a histone mark (i.e., a small fragment of histone protein) that acts as the bait to fish for readers that recognize the mark. "The key to success is not only the bait but also a specially designed hook that is equipped with a light-activated chemical group to capture the readers upon exposure to UV light," explained Professor Li.

In this study, the team focused on a methylation mark at histone H3 lysine 79 (H3K79me2). In human cells, this mark is found in actively expressed genes. Loss of H3K79me2 in mammalian embryos can lead to multiple developmental abnormalities, including impaired growth, cardiac dilation, and death. On the other hand, H3K79me2 has been found at abnormally high levels and in the wrong places (e.g., cancer-promoting genes) in a variety of cancers such as childhood leukemia.

Despite its biological significance in gene regulation, the mechanism of how this mark is "translated" is unclear, as the readers of H3K79me2 have not been found since its discovery 20 years ago. In fact, over the years, many labs have tried various approaches to look for these readers. "It is a great challenge to identify H3K79me2 readers, even with our previously developed novel chemical approaches," said Professor Li.

There are two major hurdles to overcome. First, "reading" the marks may involve not only the mark itself but also the whole histone and even the histone-DNA complex called a nucleosome. In other words, recognizing H3K79me2 by its readers may require a native nucleosome- or chromatin-context. Second, the interaction between the readers and

H3K79me2 can be weak or even transient and thereby easily lost during the fishing process.

"To capture H3K79me2 readers, we must upgrade our bait and hook," said Li. But it was not trivial. Li's lab spent more than five years developing their new tool. Instead of using a small fragment of the histone protein, they chemically synthesized an intact nucleosome with an upgraded tri-functional hook and H3K79me2 as the bait. Using this new technology, the team successfully identified a protein called menin as the reader of H3K79me2.

To understand how menin read the H3K79me2 mark, the team adopted a cutting-edge technology called cryo-electron microscopy to visualize the molecular details of this interaction. "Unraveling the details of how menin binds H3K79 methylation is key to designing new drugs to treat cancers associated with [dysregulated] H3K79me2," said Professor Li.

The pioneering work by Li and co-workers have advanced our understanding of the fundamental biological processes of gene regulation. These findings also open new opportunities for developing novel therapeutic agents to treat human diseases caused by abnormal levels of H3K79 methylation.

More information: Jianwei Lin et al, Menin "reads" H3K79me2 mark in a nucleosomal context, *Science* (2023). DOI: 10.1126/science.adc9318

Provided by The University of Hong Kong