Featured Highlight

Cracking the Structure of a Key Cancer-Related Protein

A team of researchers from The Wistar Institute, the University of Pennsylvania, and Johns Hopkins University has bettered the understanding of an enzyme that is linked to some of the deadliest human cancers.

The Marmorstein laboratory. (Bottom, from left) Michael Brent, Kimberly Malecka, Jasna Maksimoska, Brandi Sanders, Zhenyu Zhao; (middle, from left) Dario Segura Pena, Ronen Marmorstein, Katie Meeth, Peng Xie, Daniela Fera, Manqing Hong; and (top) Yong Tang.

Using x-ray crystallography at the NSLS, the researchers solved the 3-D structure of a protein called p300/CBP, which belongs to a family of enzymes known as histone acetyltransferases (HATs). These enzymes activate genes by attaching chemicals called acetyl groups to chromosomes, altering gene function.

Unlike most HATs, which regulate the expression of only a few genes, p300/CBP is involved in the activation of a wide variety of genes. Mutations in p300/CBP are linked to a variety of cancers, including pancreatic, colon, and lung cancer. And, oddly enough, p300/CBP also can suppress tumors.

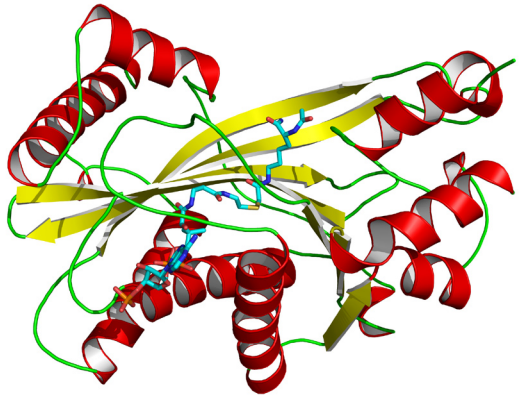
These unusual properties have made p300/CBP one of the most studied enzymes in the HAT family since a substance that selectively inhibits p300/CBP might be the basis for an anticancer drug, said Ronen Marmorstein, a Wistar researcher and a senior author on the study.

"Lots of other HATs have been well characterized, but p300 has been difficult to work with," he said. "We've been trying to crack this structure for about 10 years."

The trickiest part of the characterization process was crystallizing p300/CBP, which has a "floppy" nature, and tends to fall apart upon isolation, Marmorstein said. In 2004, one of the team's researchers discovered the reason for the protein's uncooperative behavior: in addition to acetylating histones, p300/CBP also acetylates itself. In order to prevent this self-acetylation and produce stable crystals, the researchers used a chemical that produces the protein in a form that doesn't contain acetyl groups.

Once the protein was successfully crystallized, the researchers used NSLS beamline X6A to elucidate the three-dimensional structure of a p300/CBP HAT domain, or segment, bound to a small molecule that inhibits its activity. The resulting structure revealed a number of details about its properties. First, although other enzymes are built quite differently than p300/CBP, the central region of the protein has a similar shape to other HATs.

The study also shows how the binding site and chemical mechanism of the enzyme enable it to regulate a range of genes: p300/CBP has a binding pocket that is able to link with a wide variety of substrates; and the protein uses a "hit-and-run" mechanism to attach acetyl groups to chromosomes. Other HATs tend to hang on to both the acetyl group and chromosome until the transfer is made.



Structure of the histone acetyltransferase domain of p300 bound to the Lys-CoA bisubstrate inhibitor. The protein is shown as a cartoon with α-helices, β-strands and loops shown in red, yellow and green, respectively. The Lys-CoA inhibitor is shown in CPK coloring (carbon in blue) as a stick figure.

These characteristics are well suited for designing cancer drugs capable of targeting p300/CBP without causing unwanted side effects, Marmorstein said.

Their results were published in the February 14, 2008 edition of the journal *Nature*.

Now, the scientists are working to further clarify the functions of p300/CBP, solve larger structures of the protein, and develop improved chemical inhibitors for it.

In addition to Marmorstein, coauthors on the study are Xin Liu and Kehao Zhao (Wistar), and Philip Cole, Ling Wang, Paul Thompson, and Yousang Hwang (Johns Hopkins).

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For more information, please see: X. Liu, L. Wang, K. Zhao, P.R. Thompson, Y. Hwang, R. Marmorstein, P.A. Cole, "The Structural Basis of Protein Acetylation by the p300/CBP Transcriptional Coactivator," Nature, 451, 846-850 (2008).

— Kendra Snyder