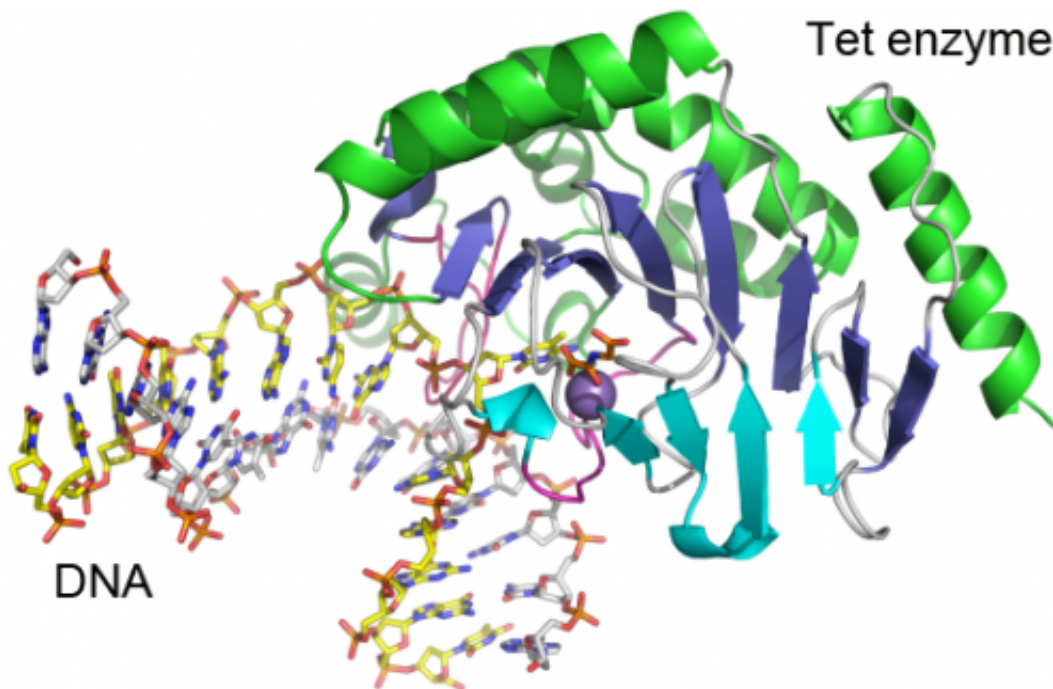


Epigenetics enigma resolved: First structure of enzyme that removes methylation

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This is the structure of the Tet enzyme with DNA. Note the purple ball at the active site, close to which one DNA base is flipped out of the double helix. Also note the degree to which the double helix is bent. Credit: Xiaodong Cheng, Emory University

Scientists have obtained the first detailed molecular structure of a member of the Tet family of enzymes.

The finding is important for the field of epigenetics because Tet

enzymes chemically modify DNA, changing signposts that tell the cell's machinery "this gene is shut off" into other signs that say "ready for a change."

Tet enzymes' roles have come to light only in the last five years; they are needed for stem cells to maintain their multipotent state, and are involved in early embryonic and brain development and in cancer.

The results, which could help scientists understand how Tet enzymes are regulated and look for drugs that manipulate them, are scheduled for publication in *Nature*.

Researchers led by Xiaodong Cheng, PhD, determined the structure of a Tet family member from *Naegleria gruberi* by X-ray crystallography. The structure shows how the enzyme interacts with its target DNA, bending the double helix and flipping out the base that is to be modified.

"This base flipping mechanism is also used by other enzymes that modify and repair DNA, but we can see from the structure that the Tet family enzymes interact with the DNA in a distinct way," Cheng says.

Cheng is professor of biochemistry at Emory University School of Medicine and a Georgia Research Alliance Eminent Scholar. The first author of the paper is research associate Hideharu Hashimoto, PhD. A team led by Yu Zheng, PhD, a senior research scientist at New England Biolabs, contributed to the paper by analyzing the enzymatic activity of Tet using liquid chromatography–mass spectrometry.

Using oxygen, Tet enzymes change 5-methylcytosine into 5-hydroxymethylcytosine and other oxidized forms of methylcytosine. 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-hmC) are both epigenetic modifications of DNA, which change how DNA is regulated without altering the letters of the genetic code itself.

5-mC is generally found on genes that are turned off or on repetitive regions of the genome. 5-mC helps shut off genes that aren't supposed to be turned on (depending on the cell type) and changes in 5-mC's distribution underpin a healthy cell's transformation into a cancer cell.

In contrast to 5-mC, 5-hmC appears to be enriched on active genes, especially in brain cells. Having a Tet enzyme form 5-hmC seems to be a way for cells to erase or at least modify the "off" signal provided by 5-mC, although the functions of 5-hmC are an active topic of investigation, Cheng says.

Alterations of the Tet enzymes have been found in forms of leukemia, so having information on the enzymes' [molecular structure](#) could help scientists design drugs that interfere with them.

N. gruberi is a single-celled organism found in soil or fresh water that can take the form of an amoeba or a flagellate; its close relative *N. fowleri* can cause deadly brain infections. Cheng says his team chose to study the enzyme from *Naegleria* because it was smaller and simpler and thus easier to crystallize than mammalian forms of the [enzyme](#), yet still resembles mammalian forms in protein sequence.

Mammalian Tet enzymes appear to have an additional regulatory domain that the *Naegleria* forms do not; understanding how that domain works will be a new puzzle opened up by having the *Naegleria* structure, Cheng says.

More information: Structure of a *Naegleria* Tet-like dioxygenase in complex with 5-methylcytosine DNA, [DOI: 10.1038/nature12905](https://doi.org/10.1038/nature12905)

Provided by Emory University

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