Tet further revealed: Studies track protein relevant to stem cells, cancer

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Last year, a research team at the University of North Carolina at Chapel Hill discovered one way the protein Tet 1 helps stem cells keep their pluripotency—the unique ability to become any cell type in the body. In two new studies, the team takes a broad look at the protein's location in the mouse genome, revealing a surprising dual function and offering the first genome-wide location of the protein and its product, 5-hydroxymethylcytosine—dubbed the "sixth base" of DNA.

UNC biochemist Yi Zhang, PhD, whose team conducted the studies, called the findings an important step in understanding the molecular mechanisms behind cell differentiation and the development of cancer. The findings appear in two recent papers, published March 30, 2011 online in *Nature* and in the April 1, 2011 issue of *Genes & Development*.

"There is no doubt that Tet proteins are relevant to cancer," said Zhang, Kenan distinguished professor of biochemistry and biophysics. Zhang is also an investigator of the Howard Hughes Medical Institute and a member of the UNC Lineberger Comprehensive Cancer Center. Tet proteins were initially discovered in leukemia as fusion proteins, which are commonly found in cancer cells, where they may function as oncoproteins.

In addition, Zhang said, "Tet is likely to be one of the important players for stem cell reprogramming." Learning to "reprogram" cells in the adult body to make them behave like stem cells has long been a goal for stem cell researchers; understanding how Tet proteins operate could help

advance stem-cell based treatments.

Tet proteins are known to help stem cells stay pluripotent. Zhang's team analyzed Tet1's occupancy across the entire mouse embryonic stem cell genome. They found that the protein works by using a two-pronged approach to maintain the mouse embryonic stem cell state.

"On one hand, it silences the genes that are important for differentiation. On the other hand, it also activates pluripotency genes," said Zhang.

The team then focused its attention on the Tet1-catalyzed reaction product,5-hydroxymethylcytosine. 5-hydroxymethylcytosine is a modified version of cytosine—the "C" in the four main DNA bases, A, T, G, and C. 5-methylcytosine and 5-hydroxymethylcytosine have been called the fifth and sixth bases of DNA, but since 5-hydroxymethylcytosine was discovered only recently, scientists know little about it.

"Everybody is trying to understand what 5-hydroxymethylcytosine is doing," said Zhang. "Is it an intermediate, or is it an end product? What is its biological function?" Zhang's team mapped the distribution of 5-hydroxymethylcytosine across the genome, offering new insights to its role in development and disease.

"It's the first time we have the whole picture of where this new modification is in embryonic stem cells," said Zhang. "We found that its role in regulating transcription is complicated. It's not simply activating or repressing genes—it depends on the context."

Like much of science, the research answers some questions while raising others. "This study is just beginning," said Zhang. Although Tet1 is known to generate 5-hydroxymethylcytosine, there are places where one exists without the other. Further investigation could reveal more about

the relationship between the two and whether other enzymes may play a role. In addition, scientists need to examine how Tet1 and 5-hydroxymethylcytosine function in animal models.

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