'BAH-code' reader senses gene-silencing tag in cells

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Greg G. Wang PhD, associate professor

University of North Carolina researchers have identified a new and evolutionarily conserved pathway to be responsible for "closing down" gene activity in the mammalian cell. The finding is closely related to the Polycomb pathway defined decades ago by a set of classic genetic experiments carried out in fruit flies.

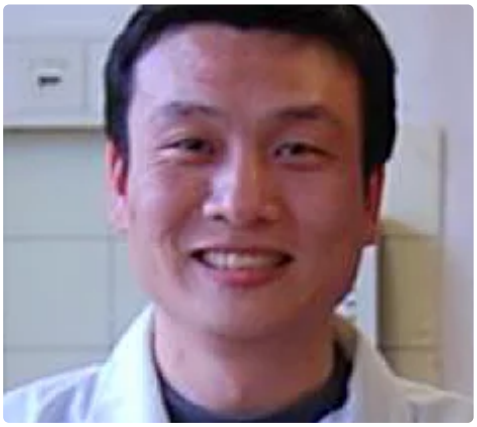
UNC Lineberger's Greg Wang, PhD, associate professor in the UNC School of Medicine Department of Biochemistry and Biophysics, and his colleagues reported in the journal Nature Genetics that the BAHCC1 protein is critically involved in silencing genes and acts as an integral component of the Polycomb gene-repressive pathway in mammalian cells.

In cells, the Polycomb pathway generates a small chemical tag, H3K27me3, to silence genes. Molecular players related to Polycomb and H3K27me3 are frequently found to be associated with pathogenesis, notably cancer and developmental syndromes.

"H3K27me3 is sort of like a gene 'tag' for silencing. Our initial interest towards BAHCC1 actually stems from a connection to cancer, in particular, leukemia. And previously, BAHCC1 was little studied," said Wang, the study's senior author. "Work on BAHCC1 turns

out to be a very interesting journey leading to fundamental understanding of Polycomb and gene silencing in general."

Huitao Fan, PhD, UNC Lineberger and UNC School of Medicine Department of Biochemistry and Biophysics, and Jiuwei Lu, PhD, University of California, Riverside, were the study's first authors.



A first author, Huitao Fan PhD postdoctoral fellow in Greg Wang lab

Leukemia is a cancer that affects the blood and bone marrow. The American Cancer Society estimated that more than 60,000 people will be diagnosed with leukemia in the United States this year, and the disease will cause more than 23,000 deaths.

In their study, researchers in Wang's lab discovered in retrospective analysis of published data that high expression of the *BAHCC1* gene was found in different types of leukemia. Using CRISPR-cas9-based state-of-the-art gene loss-of-function techniques, Wang and his team demonstrated the dependence of various acute leukemia models on BAHCC1 in progression of the disease. They determined BAHCC1 inhibits tumor suppressors to help drive acute leukemia. This function of BAHCC1 relies on an ability harbored within its protein module BAH to scan and directly bind the silencing-related tag, H3K27me3, found on the genes to be silenced

The BAH module within BAHCC1 acts as a "BAH-code (barcode)" reader for sensing the gene-silencing chemical tag, H3K27me3, in the genome of cells. (Illustration: Yuva Oz)

The team led by the other senior author of the paper, Jikui Song, PhD, University of California, Riverside, generated an atomic view of how the BAH module in BAHCC1 binds to the H3K27me3 tag.

Wang said this study challenges the current norm that tends to emphasize the previously known CBX proteins as the main effector of H3K27me3 and Polycomb silencing in mammals.

"We now realize that there exists a previously unexplored chapter of important mechanisms that animal cells use for silencing genes," Wang said. "And based on recent research of others, we believe the BAH module and related pathways are evolutionarily ancient and conserved among fungi, plants and animals. In leukemia, BAHCC1 is co-opted to silence tumor suppressive genes and to promote a cancerous program."

The researchers said they will continue to study the underlying mechanisms behind these proteins and their relationship to biology and diseases with the goal of developing therapeutic approaches.

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