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Researchers find new way to control genes often involved in cancer growth

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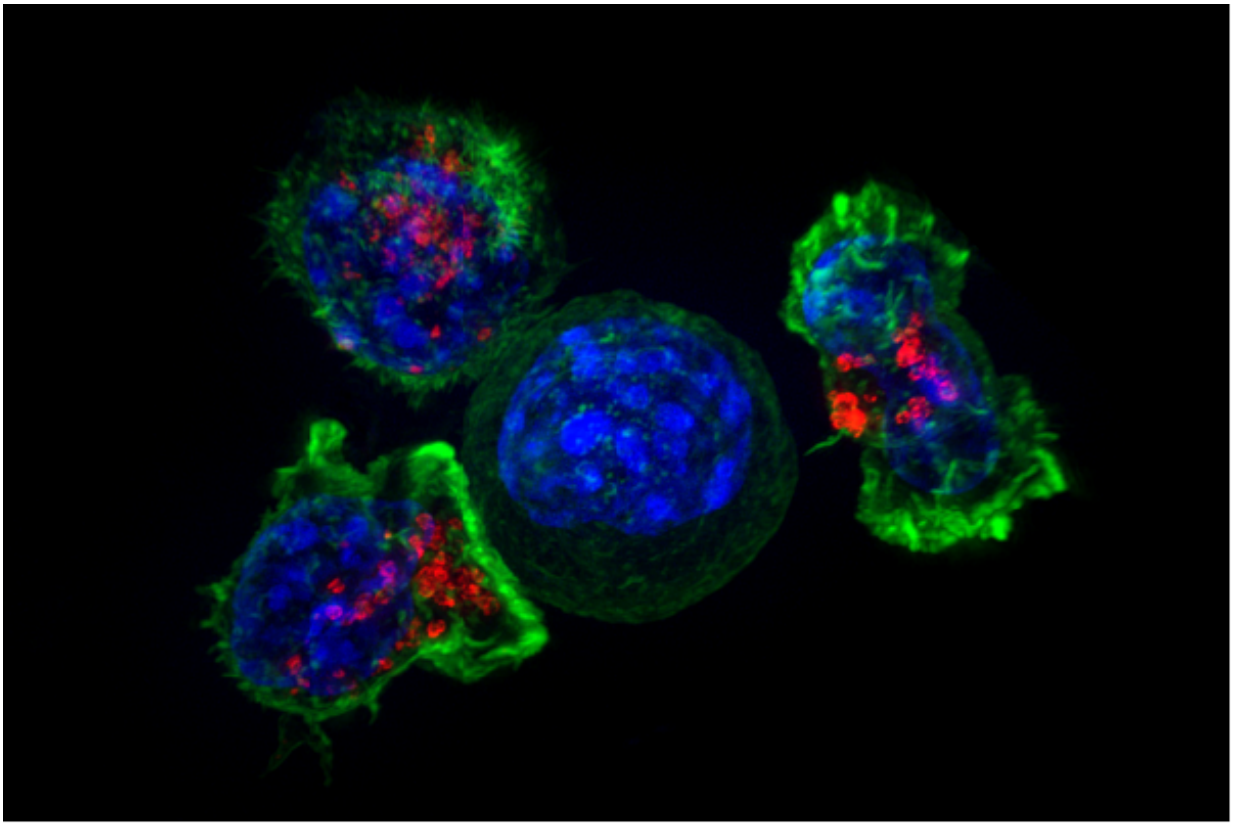

Killer T cells surround a cancer cell. Credit: NIH

Cancer is a group of more than 100 different diseases. All are driven by cells and genes that escape the normal process of division and begin their own plan to replicate in the body. Advances in genetics and molecular

biology are providing researchers with better knowledge of the genetic mutations and cell alterations that can lead to cancer, and also how to utilize that information to develop preventive measures and therapies to target the diseases.

Moffitt Cancer Center, a leader in molecular cancer research, and a research team led by Jia Fang, Ph.D., assistant member of the Tumor Biology Department, has discovered a new way to control the activity of SETDB1, a protein that is often upregulated in cancer. Their findings have been published in the June 16 issue of *Molecular Cell*.

The novel mechanism to control the protein function is called monoubiquitination. Proteins can be regulated by a process called ubiquitination, in which an ubiquitin molecule is added to a protein. Ubiquitin modification can result in a number of different effects. The addition of many ubiquitin molecules can target a protein for degradation, while the addition of a single ubiquitin molecule (monoubiquitination) can lead to activation of protein signaling pathways or target other proteins for ubiquitination. Ubiquitin is usually added to a protein through an ordered series of events - activation by an E1 enzyme, conjugation by an E2 enzyme and ligation by an E3 enzyme.

SETDB1 regulates the level of DNA compaction and gene expression. When SETDB1 is active, the expression levels of target genes are repressed. Given its critical role in controlling gene expression, SETDB1 must be precisely regulated to ensure that molecular processes run properly.

Moffitt researchers performed molecular studies to show for the first time that SETDB1 is constitutively modified by a single ubiquitin molecule. The ubiquitination event is mediated directly by E1 and E2 enzymes, without the traditional involvement of an E3 enzyme. Importantly, this monoubiquitination serves as an integral part of

SETDB1 to render its activity and leads to inhibition of target gene expression.

"This is the first demonstration that a constitutive monoubiquitination by an E2 enzyme complements the function of a key enzyme. These results suggest that this class of E2 enzymes is an attractive target for cancer therapeutics," said Fang.

More information: Lidong Sun et al, E3-Independent Constitutive Monoubiquitination Complements Histone Methyltransferase Activity of SETDB1, *Molecular Cell* (2016). DOI: 10.1016/j.molcel.2016.04.022

Provided by H. Lee Moffitt Cancer Center & Research Institute

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