Resetting the epigenetic balance for cancer therapy

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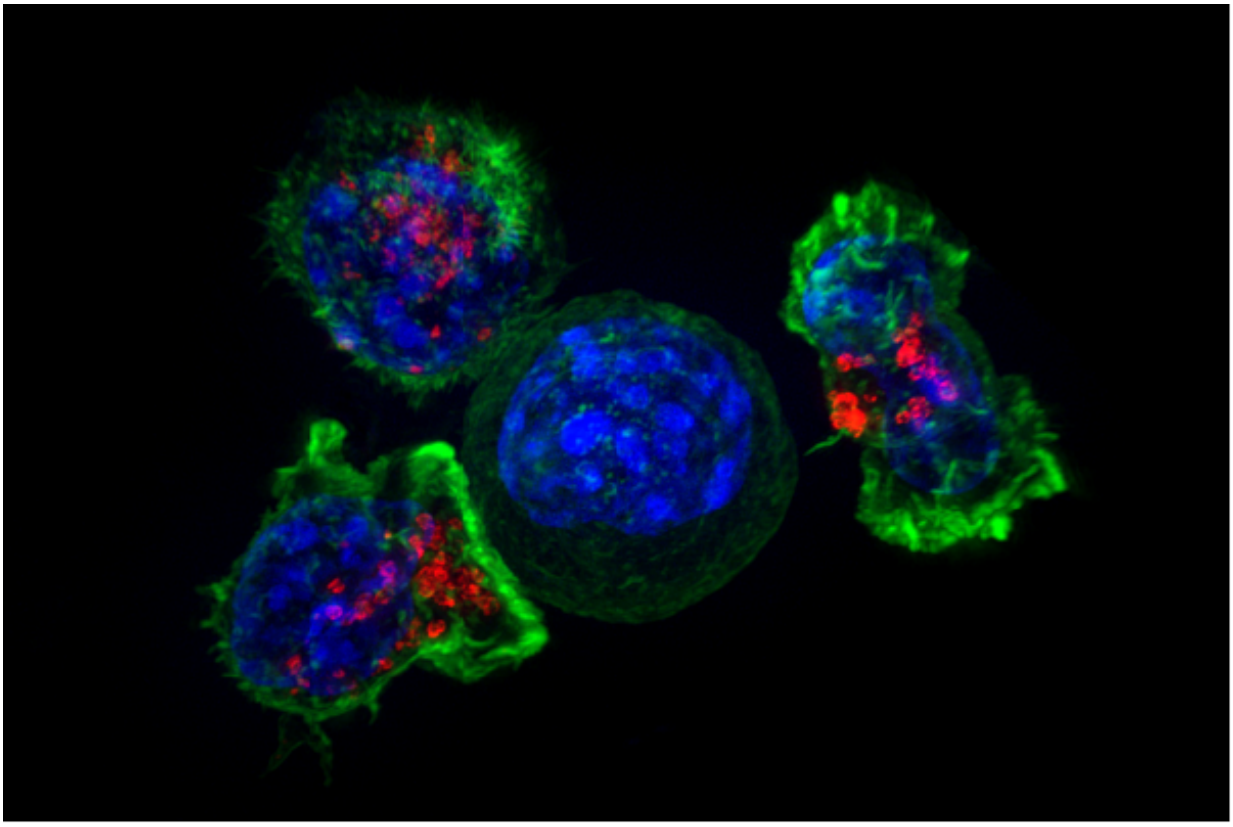

Killer T cells surround a cancer cell. Credit: NIH

Though mutations in a gene called MLL3 are common across many types of cancers, their relationship to the development of the disease has been unclear. Now, a Northwestern Medicine study has identified an

epigenetic imbalance that silences the expression of tumor-suppressing proteins, allowing cancerous cells to proliferate.

In the study published in *Nature Medicine*, Northwestern investigators applied a simple molecular inhibitor that reversed epigenetic imbalance in laboratory models. This inhibitor has a potential therapeutic application, and the study will be followed by a clinical trial led by Northwestern investigators.

"This is a simple molecular concept with major clinical significance," said Ali Shilatifard, Ph.D., director of the Simpson Querrey Center for Epigenetics, chair of Biochemistry and Molecular Genetics, Robert Francis Furchgott Professor and senior author of the study.

Mutations in MLL3, a component of a complex named COMPASS discovered by Shilatifard's laboratory, were one of the most frequently identified mutations in cancer, according to an analysis of publically available genomic data performed as part of the current study.

"Among all of the histone modifiers and transcription factors we analyzed, we found this protein was on top of the list with two significant hot-spot mutations," said Lu Wang, Ph.D., a postdoctoral research fellow in the Shilatifard laboratory and lead author on the study. "We found it was present in 7 percent of primary tumors—and in metastatic tumors, the rate of mutation was even higher."

The investigators found the presence of MLL3 hot-spot mutations was correlated with significantly lower cancer survival rates, indicating there was some oncogenic mechanism triggered by the mutations. After a series of biochemical experiments, they found success when examining the relationship between MLL3 and a molecule complex called PRC2.

MLL3, as part of COMPASS, normally promotes the expression of

numerous tumor-suppressing genes that are immediately downstream. However, the study found that if there are specific mutations in MLL3, it will not be recruited to the right location on the genome. Instead, PRC2 becomes dominant and prevents downstream tumor-suppressor gene expression.

"If you silence the tumor suppressors, you get an increased risk of tumors," Wang said.

Having identified the mechanism that leads to cancerous growth, the investigators' next effort was to interrupt the cycle. By applying a small PRC2 inhibitor, preventing PRC2 from silencing the downstream tumor-suppressor genes, the scientists were able to restore normal function and slow tumor growth.

"The balance in this mechanism was restored," Wang said. "In our models, these downstream tumor suppressors were turned on again and the tumors started to shrink in our xenograft model."

According to the authors, this pathway has therapeutic potential; Northwestern Medicine investigators have begun laying the groundwork for a clinical study. Josh Meeks, MD, Ph.D., assistant professor of Urology and co-author of the *Nature Medicine* study, will be leading a clinical trial of the method along with Maha Hussain, MD, the Genevieve E. Teuton Professor of Medicine and deputy director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The trial will treat patients with both advanced-stage bladder cancer and the MLL3 mutations with the PRC2 inhibitor, investigating if the inhibitor can improve survival rates. If it works, the implications could be significant, according to Shilatifard.

"MLL3 mutations are found in a large number of tumors," Shilatifard said. "If this works in the clinic—which our pre-clinical data suggests it will—it could have a vast application to other human cancers caused by MLL/COMPASS mutations as well."

Meeks is also an assistant professor of Biochemistry and Molecular Genetics, Hussain is also a professor of Medicine in the Division of Hematology and Oncology and Shilatifard is also a professor of Pediatrics.

Epigenetic Regulation Through Transcription

The central concept behind the *Nature Medicine* study—epigenetic errors leading to cancer—was first identified by Shilatifard's laboratory over 20 years ago. That discovery opened up a new area of inquiry, according to a new review published in *Nature Reviews Molecular Cell Biology*.

"RNA polymerase II transcribes genes, but something happens with certain mutations that make it go faster," said Shilatifard, who was senior author of the review. "The rate of elongation is increased upon mutations in cancer—we showed this 20 years ago in Science, and it has proven to be correct for a large number of cancers."

Correcting imbalance in transcription, as shown in the *Nature Medicine* study, could be put to use in other cancers as well, according to Shilatifard.

"We think this is a central dogma for future therapy," Shilatifard said.

More information: Lu Wang et al. Resetting the epigenetic balance of Polycomb and COMPASS function at enhancers for cancer therapy, *Nature Medicine* (2018). DOI: 10.1038/s41591-018-0034-6

Fei Xavier Chen et al. Born to run: control of transcription elongation by RNA polymerase II, *Nature Reviews Molecular Cell Biology* (2018). DOI: 10.1038/s41580-018-0010-5