Medical Xpress

Enzyme may be key to cancer progression in many tumors

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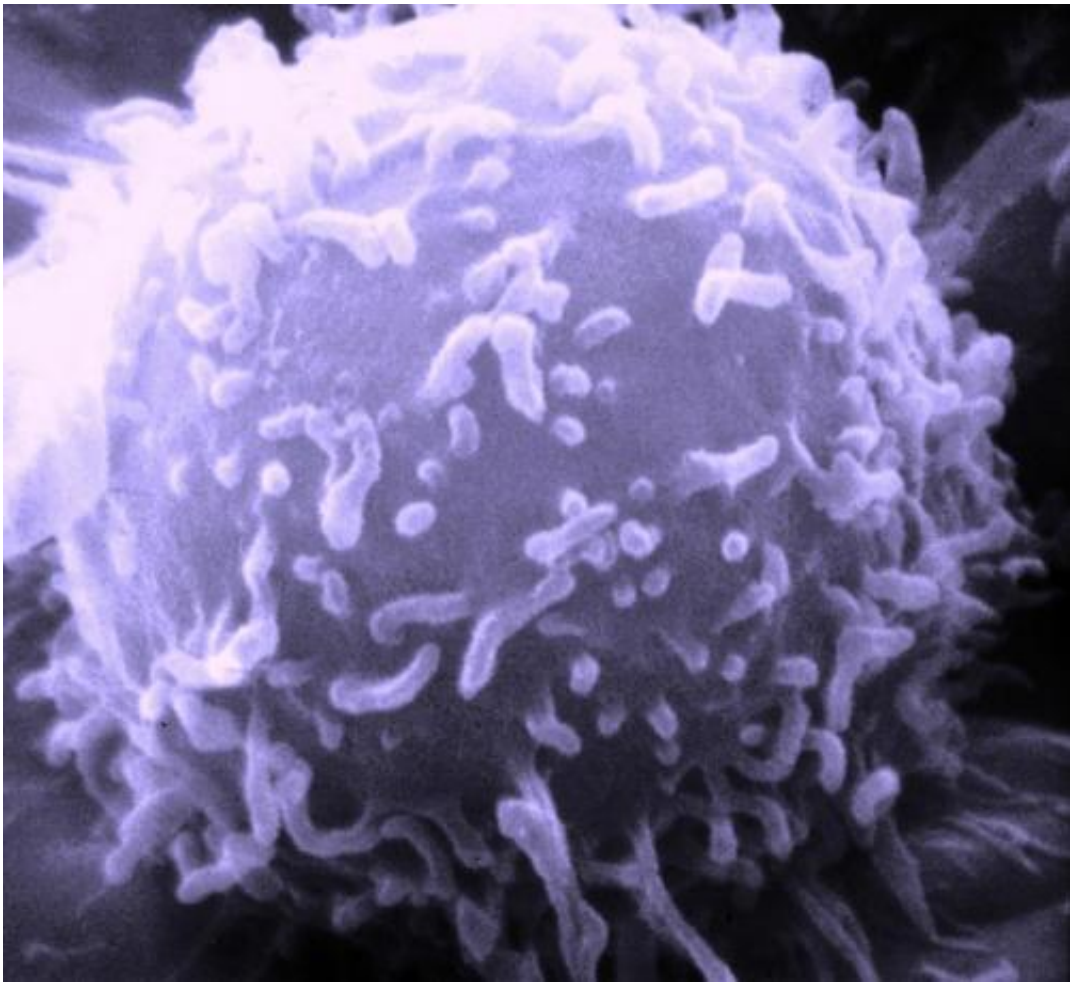

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Mutations in the KRAS gene have long been known to cause cancer, and about one third of solid tumors have KRAS mutations or mutations in the KRAS pathway. KRAS promotes cancer formation not only by driving cell growth and division, but also by turning off protective tumor suppressor genes, which normally limit uncontrolled cell growth and cause damaged cells to self-destruct.

A new University of Iowa study provided a deeper understanding of how KRAS turns off tumor suppressor genes and identifies a key enzyme in the process. The findings, published online Nov. 26 in the journal *Cell Reports*, suggest that this enzyme, known as TET1, may be an important target for cancer diagnostics and treatment.

In KRAS-driven cancers, tumor suppressor genes are turned off, or silenced, because the DNA that controls their expression is modified by methylation. The UI study shows that KRAS promotes this methylation-associated gene silencing by turning off the TET1 enzyme, which can remove methyl marks from DNA.

"We found that one of the ways tumor suppressor genes become methylated when KRAS is activated is that an 'eraser' of the methyl marks - the enzyme called TET1 - is no longer expressed," explains Charles Brenner, Ph.D., the Roy J. Carver Chair of Biochemistry in the UI Carver College of Medicine and senior study author. "This methyl eraser is normally expressed in non-malignant cells, but when KRAS is activated, the eraser is silenced, leading to accumulation of silencing methyl marks."

Cells that have become cancerous due to KRAS mutation proliferate abnormally and form colonies. Brenner and lead study author Bo-Kuan Wu, PhD, found that adding TET1 back to these cells reactivates tumor suppressor genes and is enough to reduce their abnormal proliferation. In addition, removing KRAS signaling from cancer cells reduces the cells'

malignancy, but taking TET1 away from these cells is enough to make them cancerous again, even without KRAS.

The findings, which implicate TET1 is an important player in the KRAS pathway, could help physicians decide which treatments are most likely to work for a patient's tumor.

The new study pinpoints the pathway within the KRAS biochemical cascade where the TET1 enzyme is silenced. Inhibitor drugs are available that block this pathway.

"We know that these inhibitors work in some tumors and not in others," Brenner says. "We think that the ability of an inhibitor to allow TET1 to be re-expressed may be a very strong biomarker for whether that drug will work in that tumor."

The ability to reactivate TET1 gene expression in tumor cells may also be a way to test the therapeutic potential of new compounds being developed for cancer treatment.

"We think that activating TET1 may be a general therapeutic strategy for many malignancies," Brenner says.

Provided by University of Iowa

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