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Researchers identify a rescuer for vital tumor-suppressor

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A protector for PTEN, a tumor-thwarting protein often missing in cancer cells, has emerged from research led by scientists at The University of Texas MD Anderson Cancer Center published online at *Nature Cell Biology* this week.

"We discovered that the enzyme USP13 stabilizes the PTEN protein by reversing a process that marks various proteins for destruction by the cell's proteasome," said the paper's senior author Li Ma, Ph.D., assistant professor of Experimental Radiation Oncology.

"USP13 also suppresses tumor formation and glycolysis though PTEN," Ma said. Glycolysis is a glucose metabolism pathway that tumors rely on to thrive and grow.

After establishing the relationship in cell lines and mouse model experiments, the team found low levels of USP13 in human breast tumors correlate with lower levels of PTEN. Both proteins were more abundantly present in normal breast tissue.

PTEN regulates cell growth and division. It also inhibits signaling by the AKT molecular pathway, which is involved in cell survival, metabolism and growth and is often overactive in human cancers.

This discovery provides a new way to think about PTEN deficiency and how it might be remedied. Ma noted the likely keys to possible treatment would be identifying druggable oncogenes that suppress USP13 in

cancer cells, or hitting targets usually controlled by PTEN.

"In our paper, we showed that loss of USP13 leads to loss of PTEN and activation of AKT signaling, and that treatment of a breast cancer cell line with the AKT inhibitor MK-2206 can abolish the effect of USP13 loss on promoting tumor cell proliferation," Ma said. MK-2206 is actively being tested in clinical trials against a variety of cancers at MD Anderson and elsewhere, including advanced breast cancer.

Genetic defects alone don't explain PTEN's absence

"The rationale of our work is that despite the frequent genetic alterations seen in the PTEN gene in human cancer, loss of the PTEN protein has been observed in a much higher percentage of human tumors," Ma said. "For example, approximately 5 percent of non-inherited breast tumors carry PTEN gene mutations, but loss of the PTEN protein is actually reported in nearly 40 percent of breast tumors."

This suggested, Ma said, that regulation of PTEN after gene expression or after its translation into a protein "may contribute substantially to development of human breast cancer."

Ma and colleagues focused on ubiquitylation, a process that regulates proteins by attaching molecules called ubiquitins to them. When more than one ubiquitin is attached to a protein, a chain forms that is both a target and a handle for the proteasome – a protein complex that degrades proteins and recycles bits of them for other use.

Previous studies had revealed several proteins that attach ubiquitins to PTEN to initiate its destruction. Nothing had been identified that reverses that process for PTEN.

Auditioning 30 DUBs to find one PTEN defender

The team screened 30 known deubiquitylating enzymes (DUBs). Of those, USP13 was noteworthy for its ability to stabilize PTEN by directly binding to it and removing ubiquitins.

A series of experiments showed that overexpressing USP13 in breast cancer cells:

- Increased PTEN expression and decreased cell multiplication and conversion to a cancerous state.
- Reduced cancer-promoting AKT signaling.
- Had no effect in cancer cells that lacked the PTEN gene.

The team also confirmed that USP13 removes ubiquitins from PTEN. Silencing USP13 expression tripled the polyubiquitylation of PTEN, expressing USP13 reduced it by 65 percent.

Knocking down USP13 in breast cancer cells increased cell multiplication and growth, while restoring either PTEN or USP13 completely reversed the effect.

Lower USP13, larger tumors in mice

In mice, those implanted with a breast cancer cell line with USP13 depleted had a 2.5-fold increase in tumor volume and a 3.5-fold increase in tumor weight over 65 days compared with a control group.

Ma and colleagues also analyzed USP13 and PTEN using human breast cancer progression tissue microarrays from the National Cancer Institute.

- Lower PTEN levels were found in 152 of 206 tumors (73.8 percent) and lower USP13 levels in 83 of 201 (41.3 percent).
- Of the 83 tumors with low USP13, 73 (88 percent) also had low PTEN.
- In normal breast tissue, only 31.8 percent had low levels of PTEN; 13.2 percent had low USP13.

"Our future studies aim to determine the physiological function of USP13 and how USP13 expression is lost in human cancer," Ma said.

Provided by University of Texas M. D. Anderson Cancer Center

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