# Gene may be good target for tough-to-kill prostate cancer cells

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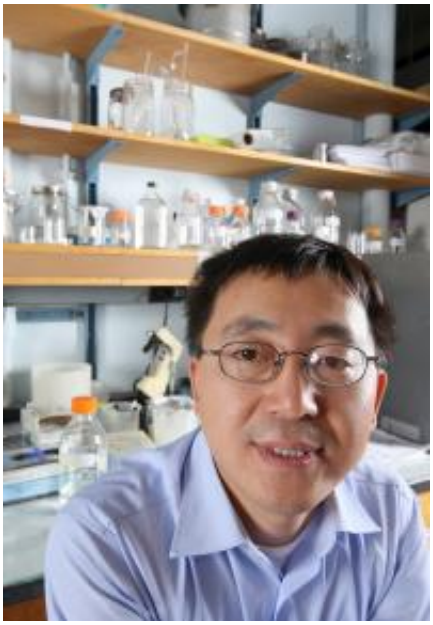

Xiaoqi Liu believes Polo-like kinase 1, a protein important in cell duplication, could be a good target for treating late-stage prostate cancers. (Purdue Agricultural Communication photo/Tom Campbell)

Purdue University scientists believe they have found an effective target for killing late-stage, metastatic prostate cancer cells.

Xiaoqi Liu, an assistant professor of biochemistry and member of Purdue's Center for Cancer Research, and graduate student Shawn Liu are focusing on the function of a gene called Polo-like kinase (Plk1), a

critical regulator of the cell cycle. Plk1 is also an oncogene, which tends to mutate and can cause cancer.

The researchers found that later-stage prostate cancer cells are missing Pten, a tumor-suppressor gene. The loss of Pten causes problems during cell division. Instead of the parent cell giving equal copies of DNA to two daughter cells, those new cells receive disproportionate amounts, causing mutations.

"This turns out to be a major driving factor in future cancer," said Xiaoqi Liu, whose findings were published in the Journal of Biological Chemistry. "Without Pten, there is huge potential to become a cancer cell."

When Pten is diminished, the cells become stressed. To compensate, they increase production of Plk1, which causes rapid cell division.

"That's usually a hallmark of cancer formation," Xiaoqi Liu said.

This particular type of later-stage prostate cancer is troublesome because the cells do not respond to drugs aimed at stopping cell division and metastatic cancers spread to other areas. When Pten is missing, Xiaoqi Liu said, those drugs actually increase the production of more Plk1.

To test the theory that Plk1 is a key to cancer formation, the researchers tested a Plk1 inhibitor called BI 2356 on both human cancer cells and mice. In both tests, some cancer cells had Pten present while others had lost it.

In both cases, the cells without Pten responded to the drug.

"In later stages of prostate cancer, cells have lost Pten," Xiaoqi Liu said. "This means the Plk1 inhibitor can be a good drug for treatment of those

tumors."

Xiaoqi Liu said tests also showed that BI 2536 could also be effective at low dosages, meaning side effects might be less severe.

Next, the researchers will try to replicate the findings in another mouse model. The National Institutes of Health funded the research.

Contributing to the research were: Timothy Ratliff, the Robert Wallace Miller Director of the Purdue Center for Cancer Research; Stephen Konieczny, a Purdue professor of biological sciences; Bennett Elzey, a Purdue assistant research professor in comparative pathobiology; Bing Song, a Purdue graduate student in biological sciences; Liang Cheng, an Indiana University professor of pathology; and Nihal Ahmad, a University of Wisconsin professor of dermatology.

**More information:** Polo-like Kinase 1 Facilitates Loss of pten-induced Prostate Cancer Formation, *Journal of Biological Chemistry*.

**ABSTRACT**
Loss of the tumor suppressor Pten (phosphatase and tensin homolog deleted on chromosome 10) is thought to mediate the majority of prostate cancers, but the molecular mechanism remains elusive. In this study, we demonstrate that Pten-depleted cells suffer from mitotic stress, and that nuclear function of Pten, but not its phosphastase activity, is required to reverse this stress phenotype. Further, depletion of Pten results in elevated expression of Polo-like kinase 1 (Plk1), a critical regulator of the cell cycle. We show that overexpression of Plk1 correlates with genetic inactivation of Pten during prostate neoplasia formation. Significantly, we find that elevated Plk1 is critical for Pten-depleted cells to adapt to mitotic stress for survival, and that re-introduction of wild-type Pten into Pten-null prostate cancer cells reduces the survival dependence on Plk1. We further show that Plk1

confers the tumorigenic competence of Pten-deleted prostate cancer cells in a mouse xenograft model. These findings identify a role of Plk1 in facilitating loss of Pten-induced prostate cancer formation, which suggests that Plk1 might be a promising target for prostate cancer patients with inactivating Pten mutations.

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