Researchers identify 'synthetic essentiality' as novel approach for locating cancer therapy targets

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Di Zhao, Ph.D. Credit: MD Anderson Cancer Center

A new method has been found for identifying therapeutic targets in cancers lacking specific key tumor suppressor genes. The process, which located a genetic site for the most common form of prostate cancer, has potential for developing precision therapy for other cancers, such as breast, brain and colorectal, say researchers at The University of Texas MD Anderson Cancer Center. Study results were published in the Feb. 6 online issue of *Nature*.

By searching for gene deletion patterns in cancer through a concept the investigators call "synthetic essentiality," the team identified a synthetic essential gene known as chromatin helicase DNA-binding factor (CHD1) as a therapeutic target for prostate and breast cancers lacking a tumor suppressor gene called phosphatase and tensin homolog (PTEN). Tumor suppressor genes are deleted in many cancers leading to tumor formation and growth.

"We searched for genes that are occasionally deleted in some cancers but which are retained in cancers caused by specific tumor suppressing genes, such as PTEN," said Di Zhao, Ph.D., Odyssey postdoctoral fellow in Cancer Biology and first author on the *Nature* paper. "We reasoned that this retained synthetic essential gene might be required for cancer-promoting actions when the cancers lose specific tumor suppressor genes."

Prostate cancer often occurs when it deletes PTEN, commonly associated with advanced prostate cancer. The Centers for Disease Control cites prostate cancer as the second leading cause of cancer-

related death for men in the U.S., with 176,000 new cases and 28,000 deaths reported annually. Up to 70 percent of primary prostate tumors are PTEN-deficient.

Through analyzing prostate cancer genome databases from The Cancer Genome Atlas and other sources, the research team found that CHD1, while occasionally deleted in some prostate cancers, was consistently retained in PTEN-deficient prostate cancer. Further investigation uncovered CHD1's role as vital to PTEN signaling, and as a potential therapeutic target in prostate and breast cancers with PTEN gene loss.

"Identifying targets essential to cell survival in tumor suppressor genes has long been an investigational goal with the aim of offering cancer-specific vulnerabilities for targeted therapy," said Ronald DePinho, M.D., professor of Cancer Biology, MD Anderson president, and senior author for the *Nature* paper. "This study provided a conceptual framework for the discovery of 'traceable' targets in cancers harboring specific tumor suppressor deficiencies."

DePinho added that further analyses are needed to verify additional synthetic essential genes in cancer cells that harbor specific genomic alterations as well as to identify potential regulatory interactions and cell-essential mechanisms.

More information: Synthetic essentiality of chromatin remodeling factor CHD1 in PTEN-deficient cancer, *Nature*, nature.com/articles/doi:10.1038/nature21357

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

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