Synthetic essentiality of chromatin remodeling factor CHD1 in PTEN deficient cancer

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Background: Prostate cancer (PCa) is the second leading cause of cancer death for men in the United States. Up to 70% of primary prostate tumors show loss of heterozygosity (LOH) at the *PTEN* locus, and loss of PTEN is a key initiation event in PCa development. Synthetic and collateral lethality have provided conceptual frameworks to identify cancer-specific vulnerabilities. Here, we explored an approach to identify potential synthetic lethal interactions through screening mutually exclusive deletion patterns in cancer genomes.

Methods: We sought to identify 'synthetic essential' genes, which might be occasionally deleted in some cancers but almost always retained in the context of a specific tumor suppressor deficiency, and posited that such synthetic essential genes would be therapeutic targets in cancers harboring specific tumor suppressor deficiencies.

Results: In addition to known synthetic lethal interactions, this approach uncovered the chromatin helicase DNA-binding factor CHD1 as a putative synthetic essential gene in PTEN-deleted cancers. In PTEN-deleted prostate and breast cancers, functional analysis showed that CHD1 depletion profoundly and specifically suppressed cell proliferation, survival and tumorigenic potential. Mechanistically, functional PTEN stimulates GSK3β-mediated phosphorylation of CHD1 degron domains, which promotes CHD1 degradation via β-TrCP-mediated ubiquitination-proteasome pathway. Conversely, PTEN deficiency results in CHD1 protein stabilization, which in turn engages the H3K4me3 mark to activate transcription of the pro-tumorigenic TNFα/NF-κB gene network. In addition, we found CHD1 depletion significantly inhibits the progression of Pten-deficient prostate cancer genetic engineered mouse model.

Conclusions: Together, this study identifies CHD1 as a novel downstream effector in PTEN pathway, and verifies CHD1 as a novel therapeutic target in PTEN deficient prostate cancer and breast cancer. Additionally, this study provides a framework for the discovery of trackable targets in cancers harboring specific tumor suppressor deficiencies.

Funding Acknowledgements: This work was supported by the Odyssey Program and Theodore N. Law Endowment For Scientific Achievement at The University of Texas MDACC (D.Z.); NIH grants R01 CA084628 (R.A.D); PCF Young Investigator Award (D.Z.)

There is no Conflict of Interest