PROSTATE CANCER

Fatal interaction: a new target identified

“depletion of β -TrCP using shRNA resulted in CDH1 accumulation and decreased ubiquitination”

A new potential therapeutic target for prostate cancer has been discovered using *in silico* analysis to identify potential synthetic-lethal gene interactions in this disease.

In this investigation, the authors established and validated an *in silico* approach for identifying potential synthetic-lethal interactions. Using information from TCGA database they searched for mutually exclusive gene deletion patterns in the cancer genome. Specifically, they sought genes that were occasionally deleted in some cancers, but were always retained if a specific gene was deleted, suggesting that it might be needed for cancer-promoting behaviour (termed synthetic-essential genes). The investigators theorized that targeting the synthetic-essential genes could inhibit the growth and survival of tumours with a specific gene mutation.

Focussing on *PTEN*, which is frequently mutated in prostate cancer, the researchers discovered a synthetic-essential relationship with *CHD1* on performing large-scale genomic analyses of data from the prostate cancer TCGA and other prostate cancer databases. A significant negative correlation between expression of *PTEN* and *CHD1* was observed between BPH and prostate cancer samples. Furthermore, *CHD1* expression positively correlated with Gleason grade and is increased in *Pten*-deficient mouse prostate epithelium, indicating that *CHD1* might be required for the progression of *PTEN*-deficient prostate cancer.

Depletion of *CHD1* using short hairpin RNA (shRNA) or CRISPR-directed nullizygous mutation in *PTEN*-deficient human and mouse prostate cancer cell lines inhibited colony formation and induced cell death. *In vivo*, suppression of *CHD1* expression reduced growth and cell proliferation and increased apoptosis of cell-line-derived xenografts in mice. In patient-derived xenograft models, treatment with *CHD1*-targeting short interfering RNA

(shRNA) inhibited tumour progression. However, these results were not recapitulated in cell lines with intact *PTEN* expression. Moreover, CRISPR-mediated knockout of *PTEN* sensitized cells to *CHD1* depletion *in vitro* and *in vivo*. *PTEN* re-expression in *PTEN*-null prostate cancer cell lines resulted in decreased *CHD1* protein expression, but did not affect mRNA levels. Furthermore, treatment with an AKT inhibitor reduced *CHD1* expression in PC3 cells and the stability of *CHD1* was increased in *PTEN*-deficient cells.

Inhibiting the proteasome in *PTEN*-wild-type BPH cells resulted in intracellular accumulation of *CHD1*. Further analysis showed that endogenous *CHD1* was modified by ubiquitination, which was enhanced by *PTEN* overexpression. Consensus-sequence scanning of E3 ligase interaction domains revealed two evolutionarily conserved putative β -TrCP consensus binding motifs, and coimmunoprecipitation experiments confirmed the interaction between β -TrCP and *CHD1*. Overexpression of β -TrCP resulted in reduced *CHD1* levels and increased its ubiquitination. Moreover, depletion of β -TrCP using shRNA resulted in *CHD1* accumulation and decreased ubiquitination. Both conserved β -TrCP binding motifs harbour a GSK3 β consensus

sequence, which is a direct target of AKT that is inhibited on AKT activation. Overexpression of GSK3 β or its constitutively active mutant *in vitro* increased *CHD1* phosphorylation and reduced its expression.

Further coimmunoprecipitation experiments showed that *CHD1* binds H3K4me3, which is associated with transcriptional activity, and a substantial reduction in this mark was observed on *CHD1* depletion *in vitro*. Chromatin immunoprecipitation followed by sequencing identified 8,468 *CHD1* binding sites and 26,826 H3K4me3-enriched regions in prostate cancer cells *in vitro*. Analysis of genes regulated by *CHD1*–H3K4me3 showed enrichment of those involved in the TNF–NF κ B pathway, which was activated in *Pten*-null mouse prostate tissue and downregulated in *CHD1*-deficient cells.

These data show that epigenetic regulation of *CHD1* is a therapeutic target in *PTEN*-deficient prostate cancer and identify a novel pathway connecting *PTEN* and the regulation of the NF κ B pathway. This *in silico* method could be used to discover other therapeutic targets in this disease.

Louise Stone

ORIGINAL ARTICLE Zhao, D. et al. Synthetic essentiality of chromatin remodelling factor *CHD1* in *PTEN*-deficient cancer. *Nature* <http://dx.doi.org/10.1038/nature21357> (2017)

Davor Pavetic / iKon Images/Getty