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Kidney Cancer

Major finding: Loss of VHL-mediated degradation of ZHX2 promotes clear cell renal cell carcinoma growth.

Mechanism: Accumulated nuclear ZHX2 interacts with RELA/p65 to drive expression of NF-κB target genes.

Impact: ZHX2 is a potential therapeutic target for patients with clear cell renal cell carcinoma.

ZHX2 IS AN ONCOGENIC DRIVER OF KIDNEY CANCER

Inactivation of the von Hippel Landau (VHL) gene, which encodes a component of the E3 ubiquitin ligase complex that mediates the degradation of prolylhydroxylated proteins, occurs in almost all patients with clear cell renal cell carcinoma (ccRCC). Hypoxia-inducible factors (HIF) are the most commonly therapeutically targeted VHL substrate; however, drug resistance frequently arises in patients treated with VEGF inhibitors, which indirectly target HIFs. To identify additional VHL targets, Zhang, Wu, and colleagues developed an *in vitro* genome-wide screening strategy to identify proteins binding with VHL complexes that are out-competed by hydroxylated, but not nonhydroxylated, HIF1α peptide. Accordingly, the zinc fingers and homeoboxes 2 (ZHX2) transcription factor was identified as a VHL substrate and shown to bind with VHL and be destabilized by VHL upon prolyl hydroxylation. Evaluation of patient samples revealed the nuclear accumulation of ZHX2 in *VHL*-deficient ccRCC but not in *VHL*–wild-type ccRCC or nontumor tissues; further, knockdown of *ZHX2* resulted in decreased VHL-deficient ccRCC proliferation and soft-agar growth *in vitro* and orthotopic ccRCC growth *in vivo*. Gene expression profiling showed that *ZHX2* depletion resulted in decreased activation of the NF-κB signaling pathway, immunoprecipitation (IP) studies showed that ZHX2 interacts with the NF-κB RELA/p65 subunit and ZHX2 also controls RELA/p65 nuclear localization. Moreover, chromatin IP-sequencing studies demonstrated the co-occupancy of ZHX2 and RELA/p65 at sites that were enriched for NF-κB consensus motifs in active promoters of genes associated with worse prognosis for patients with ccRCC. Together, these results identify and characterize ZHX2 as a VHL substrate and a potential driver of ccRCC and suggest potential therapeutic approaches for patients with VHL-deficient ccRCC. ■

Zhang J, Wu T, Simon J, Takada M, Saito R, Fan C, et al. VHL substrate transcription factor ZHX2 as an oncogenic driver in clear cell renal cell carcinoma. Science 2018;361:290–5.

Ubiquitination

Major finding: DUB3-mediated BRD4 stabilization overcomes SPOP-mediated degradation to confer BET inhibitor resistance.

Mechanism: The NCOR2–HDAC10 complex binds to and represses the *DUB3* promoter, increasing BRD4 degradation.

Impact: Therapeutic targeting of DUB3 may sensitize *SPOP*-mutant prostate cancer to BET inhibitors.

DUB3 DEUBIQUITINATES BRD4 TO PROMOTE PROSTATE CANCER PROGRESSION

BRD4 is an epigenetic reader protein in the BET family that has emerged as a therapeutic target in cancer. Prostate cancer–associated loss-of-function mutations in the E3 ubiquitin ligase SPOP impair ubiquitin-dependent proteasomal degradation of BRD4, thereby upregulating BRD4 levels and conferring resistance to BET inhibitors. It is not known whether a deubiquitinase could similarly stabilize BRD4. Jin and colleagues found that BRD4 is a substrate of the DUB3 deubiquitinase, showing that DUB3 interacted with BRD4 and specifically deubiquitinated and stabilized BRD4 in prostate cancer cells. Further, DUB3 activity suppressed SPOP-mediated BRD4 degradation. Expression of *DUB3* was suppressed by binding of the NCOR2–HDAC10 complex to the *DUB3* promoter. *NCOR2* deletion occurs in a subset of patients with castration-resistant prostate cancer (CRPC), and immunohistochemistry of 53 prostate tumor samples revealed that NCOR2 expression was inversely associated with DUB3 and BRD4 levels. Moreover, in prostate cancer cells, depletion of NCOR2 increased expression of DUB3 and BRD4. CDK4/6-mediated phosphorylation of DUB3 is required for its catalytic activity, and accordingly CDK4/6 depletion or inhibition suppressed DUB3 activity, thereby accelerating BRD4 degradation and resulting in increased levels of BRD4. Consistent with these findings, DUB3 inhibition reduced BRD4 levels and sensitized prostate cancer cells to the BET inhibitor JQ1 both *in vitro* and *in vivo* in tumor xenografts, including in *SPOP*-mutant tumors. In addition to identifying DUB3 as a BRD4 deubiquitinase, these findings suggest the potential for therapeutic targeting of DUB3 to overcome BET inhibitor resistance, especially in *SPOP*-mutant prostate cancer. ■

Jin X, Yan Y, Wang D, Ding D, Ma T, Ye Z, et al. DUB3 promotes BET inhibitor resistance and cancer progression by deubiquitinating BRD4. Mol Cell 2018 Jul 18 [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

DUB3 Deubiquitinates BRD4 to Promote Prostate Cancer Progression

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