Oncogenic enhanceosomes are disabled by p300/CBP degradation

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Background: Prostate cancer is an exemplar of an oncogenic enhancer-binding transcription factor-driven malignancy. The androgen receptor (AR) enhanceosome complex comprised of chromatin and epigenetic coregulators, assemble at enhancer elements to drive oncogenic progression. The paralog lysine acetyltransferases p300 and CBP deposit histone marks that are associated with enhancer activation. These enzymes are increasingly recognized as coregulators of AR, and their inhibition significantly hinders the growth of AR-positive prostate cancer cells, including CRPC. Despite this, the exact interplay between AR and p300/CBP within the AR enhanceosome remains elusive.

Methods: The multiomic epigenetic analyses are employed to profile the p300 and H2BNTac distribution across prostate cancer lineage-specific cistromes using ChIP-seq, RNA-seq, and ATAC-seq. We developed an orally bioavailable p300/CBP PROTAC degrader, CBPD-409, with excellent selectivity, potency, and pharmacokinetic properties to study the role of p300/CBP in the regulation of prostate cancer oncogenic enhanceosomes. Various in vitro and in vivo models are utilized to define the efficacy of CBPD-409 in suppressing prostate cancer growth.

Results: Here, we demonstrate that p300/CBP are determinant cofactors of the oncogenic AR and ERG enhanceosomes in prostate cancer. Histone H2B N-terminus multisite lysine acetylation (H2BNTac), which is exclusively reliant on p300/CBP catalytic function, marked active enhancers and was notably elevated in prostate cancer lesions relative to the adjacent benign epithelia. Degradation of p300/CBP rapidly depleted acetylation marks associated with the active oncogenic enhanceosome, which was only partially phenocopied by inhibition of their reader bromodomains. Notably, H2BNTac was effectively abrogated only upon p300/CBP degradation, which led to a stronger suppression of p300/CBP-dependent oncogenic gene programs relative to bromodomain inhibition or the inhibition of its catalytic domain. The PRISM multiplexed screening across a broad panel of cancer cell lines revealed that p300/CBP degradation is most effective in suppressing enhancer-driven cancers and levels of H2BNTac can serve as biomarkers for sensitivity to p300/CBP degradation therapy. In vivo experiments using an orally active p300/CBP proteolysis targeting chimera (PROTAC) degrader demonstrated that p300/CBP degradation potently inhibited tumor growth in preclinical models of castration-resistant prostate cancer and synergized with

AR antagonists. While mouse p300/CBP orthologs were effectively degraded in host tissues, prolonged treatment with the PROTAC degrader was well tolerated with no significant signs of toxicity.

Conclusion: Our study highlights the pivotal role of p300/CBP in maintaining the oncogenic enhanceosomes and demonstrates how target degradation may have functionally distinct effects relative to target inhibition, thus supporting the development of p300/CBP degraders preferentially impacting oncogenic enhanceosome associated with cancer while sparing normal tissues.

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