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Polycomb-independent activity of EZH2 in castration resistant prostate cancer

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Epigenetic regulators represent a new class of therapeutic targets for cancer [1]. Substantial studies suggest that the enhancer of zeste homolog 2 (EZH2) is one of such promising targets [2-4]. The current model of EZH2 oncogenic activity primarily focuses on its function as a subunit of Polycomb repressive complex 2 (PRC2), which silences gene expression via EZH2 histone methyltransferase activity [5,6].

Using a genome-wide approach we found that the oncogenic function of EZH2 in castration resistant prostate cancer (CRPC) is independent of its role as a transcriptional repressor. Instead, it involves the ability of EZH2 to act as a co-activator for critical transcription factors including the androgen receptor (AR). This functional switch is dependent on phosphorylation of EZH2, and requires an intact methyltransferase domain. Given that the loss-of-function mutations of EZH2 were observed in myelodysplastic syndrome and acute leukemia [7,8], our discovery of the non-PRC2 function of EZH2 in CRPC raises the potential to develop inhibitors that specifically target the EZH2 activation function while sparing its PRC2 repressive function to avoid the potential hematologic side effects. In addition, our finding that EZH2 cooperates with AR-associated complexes and requires phosphorylation to support CRPC growth suggests novel combination therapies for the treatment of metastatic, hormone-refractory prostate cancer.

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