Case Study

Chromatin Topology Underlies Drug Mechanism of Action

> Our research on prostate cancer was significantly enhanced by leveraging the HiChIP kit from Dovetail Genomics. It provided us with the ability to discern aberrant enhancer activation, shedding light on the underlying mechanisms driving tumor growth and response to treatment.
>
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Introduction

Prostate cancer is a leading cause of cancer-related deaths in men, and understanding the molecular mechanisms underlying its development and progression is critical for identifying potential therapeutic targets. Recent research has implicated the SWI/SNF chromatin remodeling complex, which plays a crucial role in regulating gene expression, in prostate cancer pathogenesis.

Research, from the lab of Dr. Arul Chinnaiyan at the University of Michigan, implicates "enhancer-addiction" as a key driver in some prostate cancers, relying on ectopic enhancer elements for survival and growth. The team used a combination of *in vitro* and *in vivo* experiments to investigate the role of SWI/SNF ATPases in enhancer-addiction. Using patient-derived xenograft (PDX) models and cell lines, they studied the functional consequences of inhibiting SWI/SNF ATPases using a PROTAC inhibitor.

Their findings demonstrated that SWI/SNF ATPase inhibition leads to changes in chromatin accessibility, particularly at enhancer regions, resulting in the downregulation of genes associated with prostate cancer cell survival and growth. Furthermore, they demonstrated that SWI/SNF ATPase inhibition impaired the recruitment of other oncogenic transcription factors, such as AR (androgen receptor) and FOXA1, to enhancer regions, further disrupting the enhancer-addicted state of prostate cancer cells.

The Role of Chromatin Spatial Organization

Central to the study, the team utilized HiChIP as a powerful tool to unravel the chromatin topology at known enhancer-addicted promoters linked to prostate cancer. HiChIP is a high-throughput chromosome conformation capture (3C) technique that combines chromatin immunoprecipitation (ChIP) with 3C to capture long-range chromatin interactions involving specific chromatin-binding factors of interest. This approach enables the investigation of the 3D organization of the genome

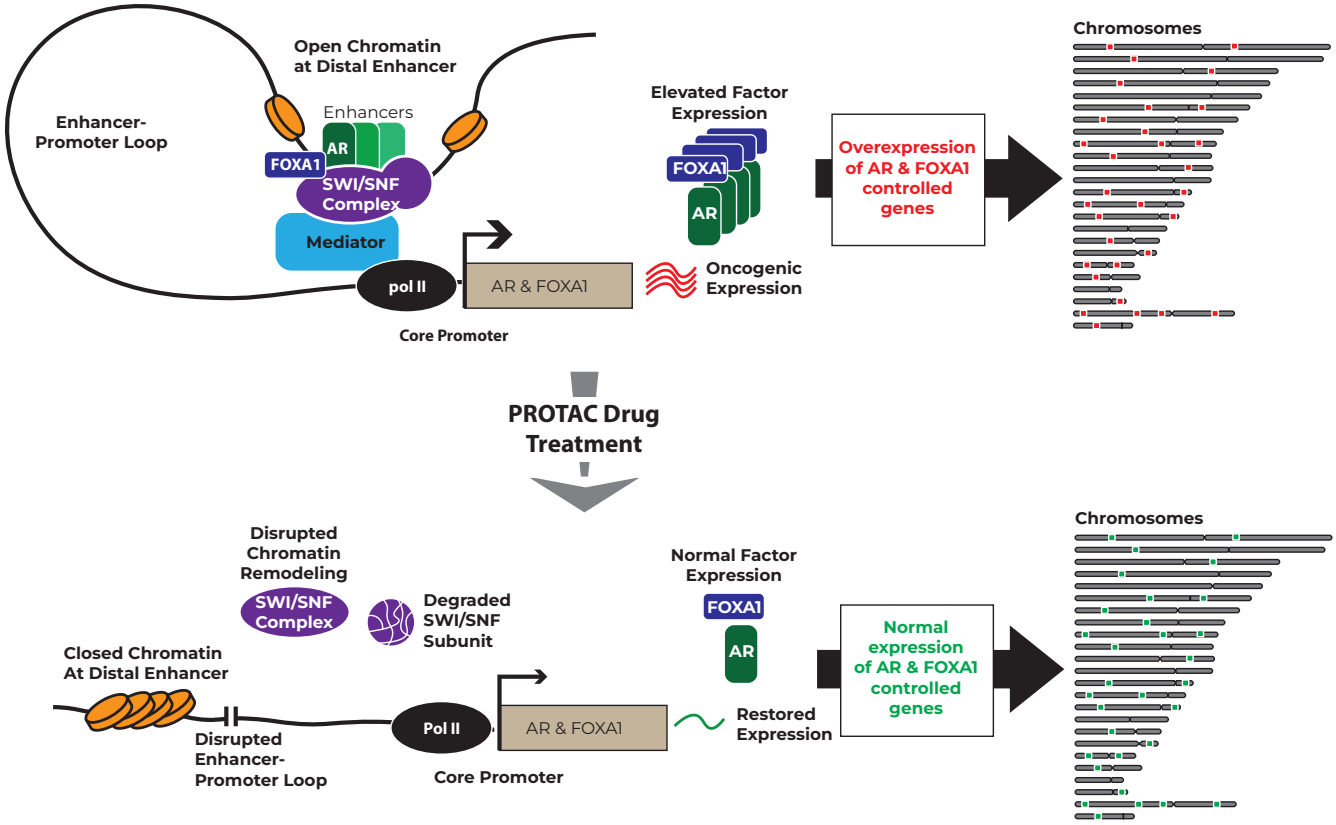

Figure 1. Ectopic ehancer activation directly interacts with the AR and FOXA1 promoters elevating gene expression. Increased AR and FOXA1 protein activates a host of downstream genes throughout the genome switching on deleterious oncogenic pathways. PROTAC directed targeted degradation of a critical subunit of the SWI/SNF complex ablates erroneously activated enhancers restoring normal gene function.

and provides insights into the spatial organization of chromatin, including the interactions between enhancer elements and their target genes.

Of note, through integration of the HiChIP data with other genomic and epigenomic datasets, such as ChIP-seq and RNA-seq, the team was able to build a more comprehensive view of the regulatory landscape in prostate cancer cells (Figure 1). This multi-omic approach enabled a deeper understanding of the interplay between chromatin topology, gene expression, and cellular function, providing valuable insights into the molecular mechanisms driving prostrate cancer development and progression.

Conclusion

This study provides valuable insights into the role of SWI/SNF ATPases in enhancer-addicted prostate cancer and highlights their potential as therapeutic targets for prostate cancer treatment. The incorporation of HiChIP data provided critical insights into the chromatin topological features driving ectopic enhancer-promoter interactions in the enhancer-addicted prostate cancer model.

The study findings suggest that inhibiting SWI/SNF ATPases can disrupt the enhancer-addicted state of prostate cancer cells, leading to anti-tumor effects. Further research in this area could potentially lead to the development of novel therapeutic strategies for prostate cancer patients.

Reference

Xiao *et al.* (2021) Nature. Targeting SWI/SNF ATPases in Enhancer-Addicted Prostate Cancer. doi.org/10.1038/s41586-021-04246-z