CHD1 loss modulates distinct AR transcriptional programs to drive prostate tumorigenesis

Augello M.A.[1,2], Liu D.[1,2,3], Deonarine L.D.[1,2], Robinson B.D.[4,5], Huang D.[1,2], Blattner M. [1,4], Doane A.S.[3], Rubin M.[2,4,5], Beltran H.[2,4,5], Elemento O.E.[3,4,5], Sboner A.[2,3,4], Dephoure N.E.[6,7], Barbieri C.E.[1,2]

1) Department of Urology
2) Sandra and Edward Meyer Cancer Center
3) Institute for Computational Biomedicine
4) Department of Pathology and Laboratory Medicine
5) Caryl and Israel Englander Institute for Precision Medicine
6) Department of Medicine
7) Department of Biochemistry
Weill Cornell Medicine, New York, NY 10065, USA

Background: Genome-wide studies have identified a high prevalence of inactivating genomic alterations associated with nucleosome remodeling enzymes, suggesting that deregulation of chromatin architecture is critical in tumor initiation/progression. While a majority of cell types appear to be dependent upon the function of these remodelers, a subclass of primary prostate cancer (PCa) is characterized by the genomic loss of a specific member of this family, CHD1. However, despite its prevalence, the consequence of CHD1 loss on transcriptional and epigenetic signaling in PCa remain incomplete. Given that PCa is a disease driven by aberrant transcriptional regulation mediated by oncogenic transcriptional factors (e.g. AR and cMYC), it is imperative to understand the molecular underpinnings of CHD1 loss driving these oncogenic programs.

Methods: Novel models of prostate-specific CHD1 loss were generated in human (CRISPR) and murine (Cre-Lox) backgrounds to define the function of CHD1 as a tumor suppressor and gatekeeper of AR signaling. The consequence of CHD1 loss on epigenetic marks, transcriptional output, and AR cistrome were assessed via RNA and ChIP sequencing, with the chromatin-bound interactome of CHD1 defined using RIME. The differences in epigenetic and AR cistromes were derived using DiffBind software, and validated against AR cistromes from primary human tumors as well as H3K27ac marks from CHD1 null clinical samples. The tumor-suppressive function of CHD1 was further validated in murine models of Chd1 loss ($Chd1^{f/f}$, $Pten^{f/f}$, Pb-Cre), aged to 1 year before resection and histological scoring.

Results: Here, we show that deletion of CHD1 drives prostate tumorigenesis and fundamentally reprograms the transcriptional program of the androgen receptor (AR), diverting AR towards an oncogenic transcriptional program and away from a growth suppressive transcriptome. Conditional deletion of Chd1 in mouse prostate resulted in prostate neoplasia in vivo, confirming Chd1 as a tumor suppressor in prostate tissue. In prostate cells, the interactome of chromatin-bound CHD1 was enriched for factors that regulate nuclear receptor function, and interrogation of the CHD1 cistrome revealed promoter-independent enrichment of CHD1 at sites specifically occupied by AR and its associated transcriptional regulators. Deletion of CHD1 resulted in a dramatic redistribution of AR across the genome, localizing AR to sites enriched for HOXB13, consistent with the AR cistrome and epigenetic marks in human prostate cancer samples. Furthermore, the CHD1 null AR cistrome was associated with a unique AR transcriptional signature, enriched for pro-oncogenic pathways and depleted for processes consistent with normal prostatic function. Collectively, these data implicate CHD1 as a prostate-specific tumor suppressor which constrains the oncogenic functions of AR though maintenance of a normal AR transcriptional program.

Conclusions: Prostate-specific loss of Chd1 drives tumor formation *in vivo*, and represents a mechanism through which the AR cistrome is rewired to engage pro-tumorigenic transcriptional programs which drive disease initiation and progression.

Conflicts of Interest: N/A

Funding: Daymon-Runyon Award (C.B), K-Award (C.B), Department of Defense Award (M.A.A), Prostate Cancer Foundation Young Investigator Award (M.A.A)