Role of CHD1 in cistrome reprogramming and prostate cancer progression

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

1. Department of Urology, Weill Cornell Medical College, New York, New York, USA.
2. Sandra and Edward Meyer Cancer Center, Weill Cornell Medicine and New York-Presbyterian, New York, NY, USA.
3. Department of Computational Biomedicine, Weill Cornell Medicine and New York-Presbyterian, New York, NY, USA.
4. Caryl and Israel Englander Institute for Precision Medicine, Weill Cornell Medicine and New York-Presbyterian, New York, NY, USA.
5. Department of Medicine, Weill Cornell Medicine, New York, New York 10021, USA.
6. Department of Biochemistry, Weill Cornell Medical College, 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 genomic loss were generated in both human (CRISPR) and murine (Cre-Lox) backgrounds in order 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 prostate resection and histological scoring.

Results: Molecular interrogation of CHD1 function in a prostate-specific background uncovered a subset of the interactome of chromatin-bound CHD1 enriched for factors that regulate nuclear receptor function. Further investigation into the CHD1 cistrome uncovered promoter-independent enrichment of CHD1 at sites specifically occupied by AR and its associated transcriptional regulators. This CHD1 binding profile is highly consistent with epigenetic marks identifying these prostate-specific enhancer sites, suggesting that CHD1 remodels enhancer-like chromatin to define a unique AR cistrome. Consistent with these observations, genomic loss of CHD1 resulted in a dramatic redistribution of AR across the genome, localizing AR to sites enriched for HOXB13 and GATA motifs, and depleting AR at AR-halfsites. These binding patterns closely mirrored those defined from the AR cistromes of human tumors, and were uniquely enriched for epigenetic marks defining these enhancers in $CHD1^{-/-}$ but not $CHD1^{+/+}$ clinical samples. Utilizing murine derived models of PCa tumorigenesis, our data demonstrate that homozygous deletion of Chd1 cooperates with loss of established tumor suppressors to drive tumor formation *in vivo*, credentialing CHD1 as a tumor suppressor in prostate tissue.

Conclusions: Prostate-specific loss of Chd1 drives tumor formation *in vivo*, and represents a potential mechanism though 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)