

Commentary

Luminal Transcription Factor Hierarchy Shapes the AR Cistrome in Prostate Cancer

Ishana Lodhia, Amina Zoubeidi *

Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; Email: Ilodhia@prostatecentre.com

* **Correspondence:** Amina Zoubeidi; Email: azoubeidi@prostatecentre.com

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Abstract

The recruitment of the androgen receptor to lineage-defining enhancers depends on the cooperation of several luminal transcription factors to facilitate opening of the chromatin; however, their pioneer function has not been fully described. In this manuscript, Keo *et al.* showed that FOXA1 alone pioneers androgen receptor recruitment while HOXB13 and GATA2 serve as cofactors, illustrating a hierarchical relationship between these TFs in AR pathway active prostate cancer (ARPC).

Keywords: AR; FOXA1; HOXB13; GATA2

The hierarchical organization of transcription factor (TF) networks is a hallmark of lineage-specific gene regulation in prostate cancer (PCa) [1]. In this context, luminal identity is primarily governed by the androgen receptor (AR), which is recruited to canonical androgen response elements (AREs) by pioneer factors [1,2]. Standard-of-care androgen deprivation therapy reprograms the AR cistrome, promoting AR pathway active prostate cancer (ARPC) [1,3]. This reprogramming shifts AR binding from canonical AREs to lineage-specific, high-affinity enhancers, coordinated in part by pioneer factors such as FOXA1, GATA2, and HOXB13 [1,3]. Despite their recognized roles, the precise requirement for each factor and the mechanisms by which they cooperate to establish and maintain the AR cistrome in ARPC remain incompletely defined.

In this issue of *Cancer Heterogeneity and Plasticity*, Keo *et al.* [4] provide compelling evidence that FOXA1 alone serves as a pioneer to remodel the chromatin and establish enhancer accessibility in ARPC, regardless of H3K4me1 enrichment. In contrast, GATA2 and HOXB13 lack independent pioneer activity and instead function as co-regulators that potentiate AR transcriptional activity at FOXA1-primed enhancers. Importantly, GATA2- or HOXB13-bound regions devoid of FOXA1 fail to recruit AR, and ectopic expression of these factors cannot rewire the AR or FOXA1 cistromes [3,4]. These findings delineate a transcriptional architecture

in which FOXA1 dictates AR enhancer targeting, with GATA2 and HOXB13 operating downstream to reinforce enhancer activation (**Figure 1**). This mechanistic insight refines our understanding of AR cistrome plasticity and may inform strategies to disrupt aberrant AR signaling in advanced disease.

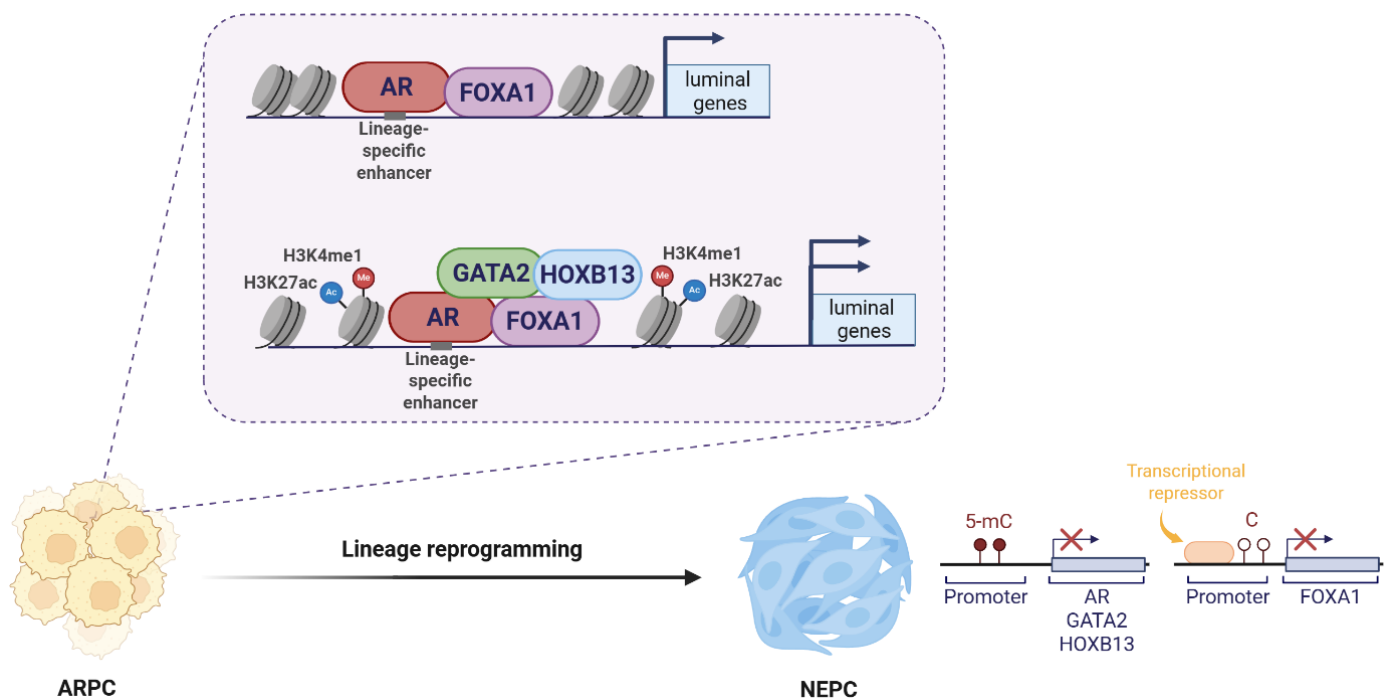


Figure 1. Role of luminal transcription factors in defining AR cistrome. In ARPC, FOXA1 alone can recruit AR to lineage-defining enhancers to activate luminal transcriptional programs. Co-binding of GATA2 and HOXB13 at H3K4me1-marked enhancers may augment FOXA1-mediated AR recruitment. Upon induction of lineage plasticity, AR, GATA2, and HOXB13 undergo time-dependent epigenetic silencing due to promoter hypermethylation. FOXA1 remains hypomethylated but may be transcriptionally repressed in NEPC.

Emerging evidence further suggests that AR itself is subject to functional reprogramming in early lineage plasticity induced by AR pathway inhibitors (ARPIs) [5]. It has been reported that the epigenetic writer EZH2 can redirect AR binding from canonical AREs to non-canonical motifs, composed of AR half-sites and FOX motifs [5]. Accordingly, the AR cistrome is reoriented toward genes associated with alternative lineage programs, hence laying the foundation for resistance. In this manuscript, the induction of lineage plasticity through FOXA2 overexpression in prostate adenocarcinoma led to a coordinated, time-dependent suppression of AR, FOXA1, HOXB13, and GATA2 [4]. Notably, downregulation of AR, HOXB13, and GATA2 was mediated by promoter hypermethylation at CpG islands (**Figure 1**). In concordance, these findings were observed in both NEPC patient-derived xenografts and clinical specimens. Surprisingly, while AR, HOXB13, and GATA2 were epigenetically silenced, FOXA1 remained hypomethylated, which suggests it is transcriptionally repressed potentially downstream of FOXA2 [6]. In FOXA2-deficient NEPC, FOXA1 is reprogrammed by neuroendocrine-specific TFs such as ASCL1 and NKX2-1 [7], further illustrating the plasticity of transcriptional circuits in advanced disease.

These findings advance our understanding of how luminal TFs regulate AR reprogramming in castration-resistant prostate cancer (CRPC). This study demonstrates that FOXA1 alone is sufficient to pioneer AR recruitment to lineage-specific enhancers, many of which lack the canonical H3K4me1 mark traditionally associated with poised or active enhancer states [4,8]. Despite prior classification of GATA2 and HOXB13 as pioneer factors, they cannot recruit AR or activate enhancers in the absence of FOXA1. This highlights a functional hierarchy among luminal TFs, wherein FOXA1 serves as the primary pioneer, while GATA2 and HOXB13 act as cofactors that enhance AR binding and transcriptional output. Although enhancer activation at AR-FOXA1-bound sites was observed regardless of H3K4me1 enrichment, the extent to which these chromatin states influence downstream AR-driven transcriptional programs remains to be fully defined.

Given that treatment with ARPIs induces widespread remodeling of the chromatin landscape during lineage plasticity [5], future studies are warranted to dissect how the epigenetic status of AR-FOXA1-bound enhancers evolves during this transition. In particular, it will be important to determine whether H3K4me1 primes genomic regions for plasticity-associated reprogramming, potentially predisposing them to alternative lineage commitment.

Declarations

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