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FOXA2, NKX2-1, and p300/CBP Orchestrate Neuroendocrine Lineage Plasticity in Prostate Cancer

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ABSTRACT

Neuroendocrine prostate cancer (NEPC) is a treatment-resistant subtype that arises through lineage plasticity, allowing tumor cells to bypass androgen receptor (AR)-targeted therapies. In a recent study, Lu et al. defined a transcriptional and epigenetic hierarchy that drives this trans-differentiation. The pioneer factor FOXA2 initiates enhancer remodeling and regional DNA demethylation, while the neural lineage transcription factor NKX2-1 is required to complete the NE program. Together, these factors reorganize 3D chromatin architecture and activate lineage-specific genes through enhancer-promoter looping. Crucially, the histone acetyltransferase p300/CBP is an essential cofactor in this process. Pharmacologic inhibition of p300/CBP with CCS1477 suppresses NE gene expression and impairs tumor growth in NEPC models. These findings offer a mechanistic insight into lineage plasticity and highlight p300/CBP as promising therapeutic targets. The study also raises key questions about the stability and reversibility of chromatin remodeling and sets a framework for understanding enhancer-driven plasticity in other cancers.

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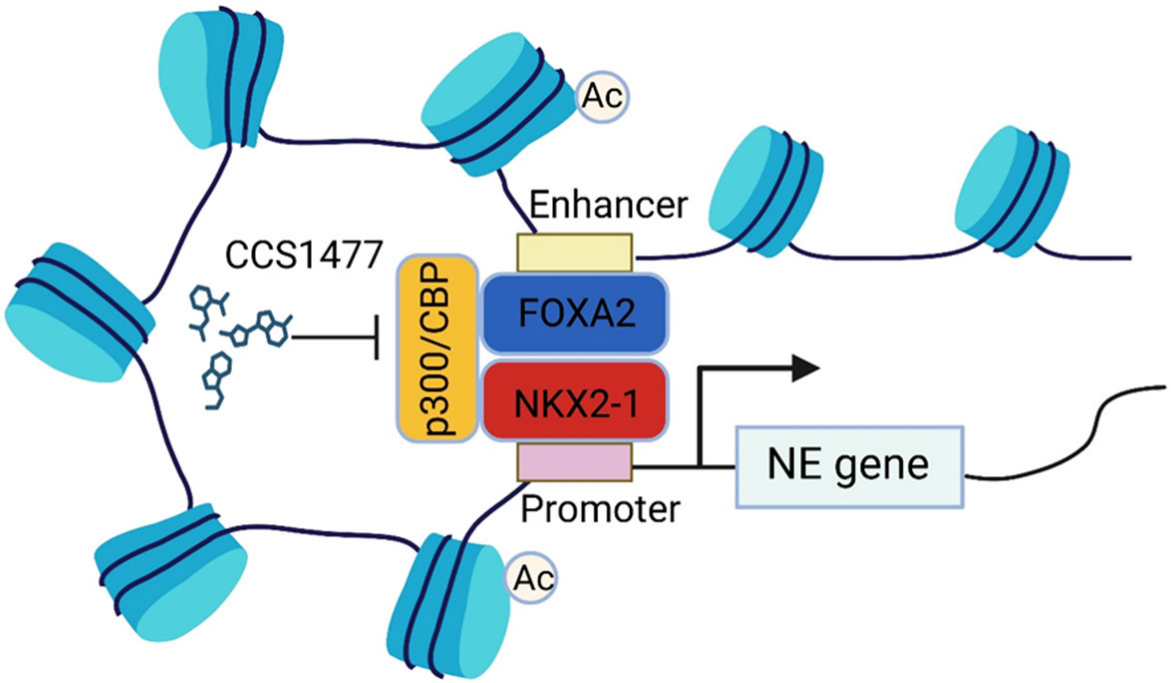
Lineage plasticity has emerged as a critical mechanism of therapy resistance in prostate cancer (PCa), enabling tumor cells to evade androgen receptor (AR)-targeted therapies by transdifferentiating into neuroendocrine prostate cancer (NEPC), a highly aggressive, treatment-refractory subtype [1, 2]. Although prior studies have defined key transcriptional and epigenetic features of NEPC, the upstream regulators and chromatin dynamics governing this phenotypic switch have remained elusive [2]. In a recent study published in *Nature Genetics*, Lu et al. identify a pivotal regulatory circuit centered on the transcription factors FOXA2 and NKX2-1, demonstrating how their coordinated activity reshapes epigenetic landscapes and reorganizes 3D chromatin structure to drive neuroendocrine trans-differentiation (NET) of prostate adenocarcinoma cells [3]. This work not only advances mechanistic insight into lineage plasticity but also highlights potential epigenetic vulnerabilities for therapeutic intervention in treatment-emergent NEPC.

Lu et al. begin by profiling chromatin architecture in patient-derived xenograft (PDX) models of castration-resistant prostate cancer (CRPC) and NEPC. Hi-C analysis reveals widespread 3D genome remodeling in NEPC, including the emergence of lineage-specific enhancer–promoter loops at key NE genes. Motif enrichment highlights FOXA2 as a candidate pioneer transcription factor enriched at newly formed chromatin loops. To investigate FOXA2 function, the authors generate a FOXA2 overexpression model in isogenic PCa cells. FOXA2 activation induces stepwise transcriptional reprogramming, accelerated tumor growth in vivo, and the acquisition of NE-like features. Bulk RNA-seq, ATAC-seq, and Hi-C across a time course reveal coordinated changes in gene expression, chromatin accessibility, and 3D chromatin topology. Single-cell RNA and ATAC profiling identify intermediate states during the transition, especially at day 14, and support a model involving both clonal transformation and selection. Mechanistically,

Figure 1. This schematic illustrates the transcriptional and epigenetic mechanisms underlying NET in PCa. The pioneer transcription factor FOXA2 binds distal enhancers and initiates chromatin accessibility, while inducing the expression of NKX2-1, a neural lineage transcription factor. FOXA2 and NKX2-1 form a cooperative transcriptional complex, engaging in enhancer-promoter looping to activate NE gene expression. The recruitment of the histone acetyltransferases p300/CBP to these sites promotes H3K-27ac deposition at lineage-defining enhancers, establishing and reinforcing the NE identity. Targeted inhibition of p300/CBP with CCS1477 disrupts this circuit and attenuates NE lineage gene expression. Created with BioRender.com



FOXA2 primes enhancer activation but depends on NKX2-1 to fully implement the NE program. FOXA2 binds distal enhancers while NKX2-1 preferentially localizes to promoters. Their co-occupancy promotes enhancer–promoter looping and activates NE gene transcription. Functional experiments show that NKX2-1 is essential for FOXA2-mediated NET. Their co-expression accelerates the transition while NKX2-1 knockdown blocks FOXA2-induced reprogramming. Using DiMeLo-seq, the authors show that FOXA2 binding correlates with regional DNA demethylation at NE enhancers in both the NEPC cell line and PDXs. These data support FOXA2's role as a pioneer factor that remodels epigenetic landscapes. Finally, mass spectrometry and ChIP-seq identify p300/CBP as a critical FOXA2–NKX2-1 cofactor. This histone acetyltransferase is required for H3K27ac deposition at NE enhancers. Genetic depletion or pharmacologic inhibition with the p300/CBP inhibitor CCS1477 suppresses NE gene expression, reduces enhancer activity, and impairs tumor growth in NEPC pre-clinical models, highlighting p300/CBP as a promising therapeutic target **(Figure 1)**.

This study by Lu et al. presents a comprehensive framework for understanding NET. By elucidating the cooperative actions of the pioneer factor FOXA2 and neural lineage transcription factor NKX2-1, the authors define a feed-forward transcriptional and epigenetic circuit that drives NET. Their model highlights how enhancer priming, DNA demethylation, and 3D chromatin reorganization are not parallel events, but rather coordinated steps orchestrated by transcription factor hierarchies.

A key conceptual advance lies in the dissection of temporal chromatin dynamics. FOXA2 overexpression initiates regional DNA demethylation at lineage-defining enhancers, a hallmark of pioneer factor activity. This is followed by deposition of H3K4me1 and eventual activation of enhancers by NKX2-1 and the histone acetyltransferase p300/CBP. These changes culminate in new enhancer–promoter loops that stabilize NE lineage programs. The authors also suggest that these chromatin alterations may constitute a form of epigenetic memory, locking in NE identity in a manner that is difficult to reverse, an insight with clear therapeutic implications.

Another strength of the study is the use of multiomic, time-resolved data to define intermediate stages of NET. Single-cell analyses reveal that the shift from AR-positive, luminal-like cells to AR-negative, NE-like cells occurs via intermediate chromatin and transcriptomic states. These transitional cells exhibit mixed lineage features, implicating the stepwise reprogramming rather than abrupt fate switching. Notably, clonal dynamics show that both transformation and expansion contribute to NET, reinforcing the model's biological relevance.

The identification of NKX2-1 as a FOXA2-induced effector adds a layer of complexity. NKX2-1 not only binds promoter regions of NE genes but also reinforces FOXA2 binding through chromatin looping, establishing a self-reinforcing regulatory loop. The data suggest that NKX2-1 can act through multiple pioneer factors. While it cooperates with FOXA2 in a subset of NEPC tumors, it may also function with ASCL1 in FOXA2-low tumors. This functional flexibility pinpoints the central role of NKX2-1 in NEPC fate determination. Perhaps the most clinically impactful is the demonstration that p300/CBP activity is essential for NEPC enhancer activation. The p300/CBP inhibitor CCS1477 disrupts FOXA2/NKX2-1, dependent transcriptional programs, and suppresses tumor growth in NEPC preclinical models. While CCS1477 does not reverse NET, its selective inhibition of NE enhancers offers a promising therapeutic strategy for NEPC tumors that are enhancer-addicted. Importantly, CCS1477 also inhibits AR-driven transcription, raising the possibility of dual efficacy in mixed or transitioning tumors.

These findings align with broader mechanisms in lineage plasticity. NKX2-1 acts as a lineage-survival factor in small cell lung cancer [4], and FOXA family transcription factors regulate chromatin remodeling in pancreatic [5] and breast cancers [6]. The consistent co-expression and mutual dependence of FOXA2 and NKX2-1 in NEPC also suggest potential value as diagnostic or prognostic biomarkers. Whether the epigenetic state established by FOXA2 is reversible or whether other pioneer factors can substitute in different tumor genotypes remains to be determined. However, the data strongly support a lineage-restricted, non-redundant role for FOXA2 in PCa plasticity.

In conclusion, the study by Lu et al. establishes a mechanistic blueprint for lineage plasticity in PCa, revealing how the pioneer factor FOXA2 and neural lineage TF NKX2-1 cooperate to remodel the epigenome and enforce neuroendocrine identity. The reliance of this process on p300/CBP-mediated enhancer activation uncovers a promising therapeutic axis in NEPC. Future studies should explore whether this transcriptional hierarchy operates across NEPC subtypes and determine the durability or reversibility of FOXA2-mediated epigenetic remodeling. Understanding the timing and sequence of chromatin reorganization may inform strategies for early detection or therapeutic interruption of lineage transition. More broadly, this work provides a generalizable model of how transcription factor hierarchies, enhancer reprogramming, and chromatin topology collaboratively drive tumor plasticity and resistance. This not only applies to treatment-emergent NEPC but also as a reference for investigating how transcription factor-driven chromatin remodeling underlies lineage switching in other solid tumors.

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Declaration of interests

The author has no conflict of interest to declare.

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