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HOXB13 as a Lineage-Restricted Chromatin Regulator Linking Androgen Signaling, Epigenetic Remodeling, Metabolic Reprogramming, and Kinase Signaling in Prostate Cancer Progression

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ABSTRACT

Prostate cancer progression is shaped by dynamic interactions among lineage identity, androgen receptor signaling, chromatin organization, metabolic adaptation, and therapy-induced plasticity. HOXB13 is a prostate-enriched homeobox transcription factor classically recognized for its roles in prostate development, androgen receptor transcriptional regulation, and hereditary prostate cancer susceptibility. However, emerging evidence indicates that HOXB13 functions beyond lineage specification. HOXB13 organizes prostate-specific transcriptional programs, shapes androgen receptor cistromes, regulates AR-variant activity in castration-resistant prostate cancer, and controls chromatin-dependent metabolic gene expression. In advanced disease, HOXB13 activity may be further reshaped by altered androgen receptor signaling, cofactor switching, mutation, and post-translational modifications, including acetylation and phosphorylation. These regulatory layers suggest that HOXB13 expression alone may be insufficient to define its function; rather, HOXB13 may exist in distinct post-translationally modified functional states that influence AR/luminal identity, lipid metabolism, glycolytic-hypoxic adaptation, lineage plasticity, and therapeutic vulnerability. In this review, we discuss HOXB13 as a lineage-restricted chromatin-metabolic regulator in prostate cancer and highlight kinase-dependent regulation as an emerging area for future investigation.

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1. Introduction

Prostate cancer is a lineage-dependent malignancy in which tumor initiation, progression, and therapeutic response are strongly influenced by androgen receptor signaling and prostate epithelial identity [1-5]. Although recurrent genomic alterations such as PTEN loss, MYC amplification, ETS rearrangements, SPOP mutation, TP53 loss, RB1 loss, and AR amplification contribute to disease heterogeneity, lethal prostate cancer is also driven by transcriptional and epigenetic adaptation [6-13]. In many cases, progression to castration-resistant prostate cancer does not reflect complete independence from androgen receptor signaling, but rather a reorganization of androgen receptor activity, chromatin accessibility, enhancer usage, and lineage transcriptional networks [7-15].

Androgen deprivation therapy remains the therapeutic backbone for advanced prostate cancer and is typically achieved through surgical castration or medical suppression of testicular androgen production using luteinizing hormone-releasing hormone agonists or antagonists, often with antiandrogen therapy. Despite effective suppression of circulating testosterone, most patients with advanced recurrent disease eventually develop castration-resistant prostate cancer. This transition is frequently accompanied by rising serum prostate-specific antigen, indicating that tumor growth often remains dependent on androgen receptor signaling despite castrate androgen levels. Mechanistically, persistent androgen receptor activity in CRPC can arise through androgen receptor overexpression or amplification, ligand-independent androgen receptor activation, androgen receptor splice variants, altered androgen receptor chromatin binding, and increased intratumoral androgen synthesis [16]. These observations provided the rationale

for developing next-generation androgen receptor pathway inhibitors that more effectively suppress androgen receptor signaling. Enzalutamide, a potent androgen receptor inhibitor, significantly improved radiographic progression-free survival and overall survival in men with chemotherapy-naïve metastatic CRPC in the phase III PREVAIL trial, supporting continued dependence on androgen receptor signaling in a substantial subset of castration-resistant tumors [16]. Similarly, abiraterone acetate, which suppresses androgen biosynthesis through CYP17A1 inhibition, further demonstrated that targeting residual androgen receptor pathway activity improves outcomes in advanced prostate cancer [17, 18].

However, tumors frequently escape androgen deprivation therapy and next-generation androgen receptor pathway inhibitors, including enzalutamide and abiraterone acetate, through multiple mechanisms, including androgen receptor amplification, enhancer amplification, intratumoral androgen synthesis, ligand-independent androgen receptor activation, expression of androgen receptor splice variants, and lineage plasticity. Some tumors remain androgen receptor-driven, whereas others acquire androgen receptor-indifferent, basal-like, stem-like, or neuroendocrine-like features. These transitions are accompanied by extensive remodeling of chromatin state and cellular metabolism [7-15, 19-21].

Metabolic reprogramming is now recognized as a critical feature of prostate cancer progression. Normal prostate epithelial cells have a specialized metabolic program characterized by zinc accumulation and citrate secretion. Malignant transformation disrupts this program and promotes mitochondrial activity, lipid synthesis, cholesterol metabolism, and biosynthetic growth [22-27]. During progression to castration resistance and therapy-refractory disease, prostate cancer cells may further adapt through altered de novo lipogenesis, lipid droplet accumulation, oxidative metabolism, glycolysis, hypoxia signaling, mitochondrial rewiring, and stress-survival pathways [28-36]. These metabolic changes are not simply downstream consequences of oncogenic signaling; they are also shaped by lineage transcription factors and chromatin regulators that determine which metabolic enhancers are accessible, acetylated, and transcriptionally active [37].

HOXB13 is positioned at this intersection. HOXB13 is a prostate-enriched homeobox transcription factor involved in prostate development, prostate epithelial identity, androgen receptor transcriptional regulation, and hereditary prostate cancer susceptibility [38-43]. Genome-wide studies have shown that HOXB13 cooperates with lineage-associated factors such as FOXA1 and GATA2 to shape androgen receptor chromatin binding and prostate-specific transcriptional output. In castration-resistant disease, HOXB13 also regulates AR-V7 cistromes, suggesting that its influence extends beyond canonical ligand-dependent androgen receptor signaling [44-49].

Recent findings have expanded HOXB13 biology into metabolism. HOXB13 suppresses de novo lipogenesis through HDAC3-mediated epigenetic repression; loss of HOXB13 or the G84E mutation activates lipogenic programs, increases lipid accumulation, promotes motility, and enhances metastasis [50]. Additional studies suggest that loss of HOXB13-mediated repression may shift enhancer activity toward p300/CBP-dependent activation, creating targetable metabolic and metastatic vulnerabilities [51]. These observations support a model in which HOXB13 is not simply a lineage marker or androgen receptor cofactor, but a chromatin-metabolic regulator that couples prostate identity to metabolic state.

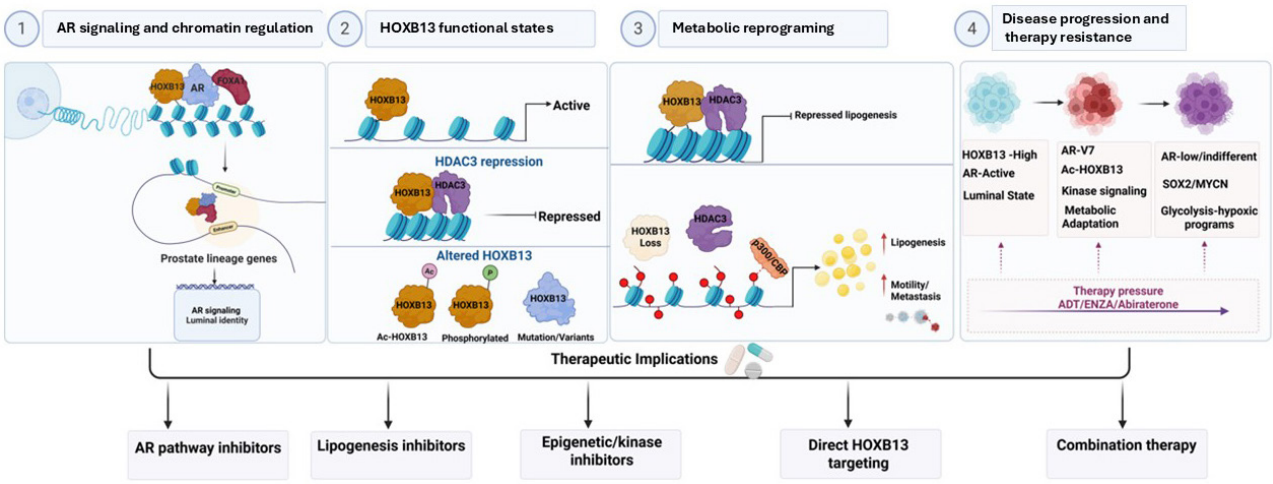
A further emerging concept is that HOXB13 function may be regulated by post-translational modifications. Acetylation of HOXB13 has been linked to super-enhancer-associated transcriptional programs in CRPC, and mTOR-mediated phosphorylation has been reported to regulate HOXB13 activity and oncogenic function [52, 53]. These findings suggest that HOXB13 output may be controlled by upstream signaling pathways. Because kinase signaling is frequently altered in advanced prostate cancer, additional kinases, including PLK1, may be relevant to HOXB13 functional states.

This review proposes a unifying model: HOXB13 functions as a context-dependent transcriptional scaffold that integrates androgen receptor signaling, enhancer regulation, epigenetic cofactors, metabolic programs, and signaling-dependent post-translational control. Alteration of HOXB13 expression, mutation status, stability, acetylation, phosphorylation, or cofactor interaction may shift prostate cancer cells between AR/luminal identity, lipogenic growth, glycolytic-hypoxic adaptation, and lineage-plastic states.

2. HOXB13 in Prostate Lineage Identity and Hereditary Prostate Cancer Risk

HOXB13 belongs to the HOX family of homeobox transcription factors, which regulate developmental patterning, positional identity, and tissue differen-

Figure 1. HOXB13-centered regulatory networks in prostate cancer progression and therapeutic resistance.



1. AR signaling and chromatin regulation: HOXB13 cooperates with AR and FOXA1 at regulatory chromatin regions to support prostate lineage gene expression, AR signaling, and luminal identity.
2. HOXB13 functional states: HOXB13 activity is shaped by chromatin context, cofactor interactions, acetylation, phosphorylation, and mutation or variant-associated alterations. These states may determine whether HOXB13 supports active transcription, HDAC3-mediated repression, or altered transcriptional programs.
3. Metabolic reprogramming: Intact HOXB13 recruits HDAC3 to restrain lipogenic enhancer activity and suppress de novo lipogenesis. In contrast, HOXB13 loss or impairment reduces HDAC3-mediated repression, permits p300/CBP-associated enhancer activation, increases lipogenic output, and promotes motility and metastatic phenotypes.
4. Disease progression and therapy resistance: Under therapy pressure from androgen deprivation therapy, enzalutamide, or abiraterone, prostate cancer may progress from AR-active luminal states toward CRPC and lineage-plastic or AR-indifferent states characterized by AR-V7, altered HOXB13 states, metabolic adaptation, SOX2/MYCN-associated plasticity, and glycolytic-hypoxic programs.
Conclusion: Together, these HOXB13-associated regulatory states suggest therapeutic opportunities involving AR pathway inhibitors, lipogenesis inhibitors, epigenetic or kinase inhibitors, direct HOXB13-targeting approaches, and rational combination therapy.

tiation [38, 39]. In the prostate, HOXB13 is highly enriched and contributes to epithelial differentiation and prostate-restricted transcriptional programs. Its expression pattern has also made HOXB13 useful as a marker of prostatic origin, particularly in metastatic lesions where other prostate markers may be reduced [38, 42, 43].

The clinical importance of HOXB13 was strengthened by the discovery of germline HOXB13 mutations in hereditary prostate cancer. The G84E variant was identified in families with hereditary prostate cancer and is associated with increased prostate cancer risk, particularly in men of European ancestry [40-42]. Although HOXB13 mutations account for only a minority of prostate cancer cases, they provide direct genetic evidence that alteration of a prostate-enriched transcription factor can influence disease susceptibility.

HOXB13 function is also shaped by its interaction with transcriptional cofactors. Brechka and colleagues highlighted that germline HOXB13 mutations, particularly G84E, brought HOX signaling into focus as a clinically relevant pathway in hereditary prostate cancer. Beyond mutation status, they emphasized that HOX protein function depends heavily on binding partners and cofactors that regulate DNA-binding specificity and transcriptional output. This concept is important for prostate cancer because HOXB13 does not act as an isolated transcription factor. Rather, its biological effects are shaped by interactions with the androgen receptor, FOXA1, and other context-dependent chromatin regulatory proteins. Therefore, HOXB13 mutations or altered cofactor interactions may reshape prostate lineage transcription, chromatin organization, and disease progression [54].

The importance of HOXB13-associated cofactors is further supported by studies of MEIS1 and MEIS2, two HOX-interacting proteins implicated in prostate cancer progression. Bhanvadia and colleagues re-

ported that MEIS1 and MEIS2 expression decreases stepwise from benign prostate epithelium to localized prostate cancer and metastatic disease, while retention of MEIS expression in primary tumors is associated with reduced risk of biochemical recurrence and clinical metastasis. These findings suggest that loss of specific HOX-associated cofactors may weaken differentiation-associated transcriptional programs and promote metastatic progression. In the context of HOXB13 biology, MEIS1 and MEIS2 support the broader concept that HOXB13 output is shaped not only by HOXB13 expression or mutation status, but also by the availability of lineage-associated binding partners [55].

The biological consequences of HOXB13 alteration are complex. Early studies suggested that HOXB13 can repress hormone-activated androgen receptor signaling in some contexts [43]. Later work demonstrated that HOXB13 regulates androgen-responsive transcription more broadly and influences cellular responses to androgen stimulation [44]. Genome-wide studies subsequently revealed that HOXB13 participates in tumor-specific androgen receptor cistrome remodeling [45]. Together, these studies indicate that HOXB13 is not a static lineage marker. It is an active regulator of transcriptional state.

HOXB13 function may appear paradoxical because it can be associated with both tumor-promoting and tumor-restraining activities. In androgen receptor-driven prostate cancer, HOXB13 can support prostate-lineage transcriptional programs and androgen receptor-associated transcription. In contrast, HOXB13 can suppress lipogenic reprogramming and metastatic phenotypes through HDAC3-dependent repression [50]. This duality likely reflects context-dependent transcription factor function. HOXB13 output depends on disease stage, androgen receptor status, chromatin accessibility, cofactor availability, mutation state, and post-translational modification. Therefore, HOXB13 should not be classified simply as an oncogene or tumor suppressor. A more accurate model is that HOXB13 defines context-specific functional states.

3. HOXB13 as an Organizer of Androgen Receptor Signaling and Cistrome Reprogramming

Androgen receptor signaling is the dominant lineage-defining transcriptional axis in prostate cancer. Upon androgen binding, the androgen receptor binds regulatory DNA elements and controls genes involved in differentiation, secretory function, survival, proliferation, and metabolism [1-5]. However, the androgen receptor does not function autonomously. Its genomic occupancy and transcriptional output are determined by the chromatin landscape, pioneer factors, lineage transcription factors, enhancer accessibility, histone modifications, and enhancer-promoter interactions [44-50].

HOXB13 is a central component of this androgen receptor-regulatory architecture. Early mechanistic studies showed that HOXB13 physically and functionally interacts with the androgen receptor and modulates androgen-responsive transcription [44, 45]. Norris and colleagues demonstrated that HOXB13 regulates cellular responses to androgens and interacts with the androgen receptor DNA-binding domain, supporting a model in which HOXB13 influences the specificity and magnitude of androgen receptor target gene regulation [44]. Importantly, HOXB13 can activate or repress specific androgen receptor-regulated genes depending on genomic context, indicating that its function is locus-specific rather than uniformly activating or inhibitory.

Genome-wide cistrome studies provided a major advance in understanding HOXB13 function. Pomerantz and colleagues showed that the androgen receptor cistrome is extensively reprogrammed during human prostate tumorigenesis [45]. Tumor-reprogrammed androgen receptor binding sites were enriched for FOXA1 and HOXB13, and expression of FOXA1 and HOXB13 in immortalized prostate epithelial cells was sufficient to shift androgen receptor binding toward a tumor-like pattern [45]. This finding established HOXB13 as an active organizer of androgen receptor enhancer selection during transformation.

The cooperation between HOXB13 and FOXA1 highlights a broader principle of prostate cancer transcriptional control. FOXA1 functions as a pioneer factor capable of binding compacted chromatin and facilitating nuclear receptor access, whereas HOXB13 provides prostate lineage specificity and may stabilize or redirect androgen receptor occupancy at selected loci [47-49]. GATA2 and other lineage-associated factors further contribute to androgen receptor transcriptional output. Together, these factors define a prostate-specific enhancer grammar in which androgen receptor binding is guided by pre-existing lineage architecture.

In castration-resistant prostate cancer, HOXB13 remains relevant because androgen receptor signaling often persists despite androgen deprivation. One

major mechanism is expression of androgen receptor splice variants such as AR-V7, which lacks the ligand-binding domain and can drive ligand-independent transcription. Chen and colleagues showed that diverse AR-V7 cistromes in CRPC are governed by HOXB13 [49]. This suggests that HOXB13 can influence not only canonical full-length androgen receptor binding but also androgen receptor variant-driven programs in advanced disease.

Consistent with this concept, the ACK1–AR and AR–HOXB13 signaling axes have been proposed as epigenetic regulatory pathways contributing to lethal prostate cancer. In this model, androgen deprivation increases the dependence of CRPC cells on alternative survival and transcriptional programs, including ACK1- and HOXB13-associated pathways. HOXB13 is particularly relevant because its interaction with AR can influence AR and AR-V7 chromatin binding in metastatic CRPC, linking lineage-restricted transcriptional regulation to therapy-resistant androgen receptor signaling [56].

These findings place HOXB13 at a critical boundary between lineage maintenance and adaptive transcriptional plasticity. In one context, HOXB13 preserves prostate-lineage androgen receptor transcriptional identity. In another context, it may allow advanced tumors to reorganize androgen receptor signaling under therapeutic pressure. Thus, HOXB13 should be viewed as an architectural regulator of androgen receptor signaling, enhancer selection, and prostate cancer transcriptional state.

4. HOXB13 and Chromatin Remodeling: Enhancer Selection, Cofactor Balance, and Functional State

Transcription factors exert their biological effects through chromatin. They bind regulatory elements, recruit cofactors, modify local histone marks, influence enhancer-promoter communication, and organize transcriptional networks. HOXB13 functions within this chromatin ecosystem.

The androgen receptor cistrome reprogramming work established HOXB13 as a determinant of enhancer selection [45]. However, enhancer selection alone does not determine whether a bound site becomes active or repressed. That outcome depends on cofactor recruitment, histone modifications, nucleosome positioning, and chromatin remodeling enzymes. HOXB13-associated cofactors therefore represent a critical layer of regulation.

The HOXB13-HDAC3 axis provides a mechanistic example. HDAC3 is a histone deacetylase that participates in transcriptional repression at selected loci. Recent work further supports the idea that HDAC3 can modulate androgen receptor-associated regulatory elements in a context-dependent manner. Chen and colleagues reported that canonical androgen response element motifs can function as growth-suppressive regulatory elements in prostate cancer cells and that HDAC3 preferentially associates with ARE-enriched AR-bound chromatin after androgen stimulation [57]. In this setting, HDAC3 appeared to restrict the growth-suppressive transcriptional program induced by ARE activation, whereas HDAC3 disruption enhanced AR/ARE-associated activity and impaired cell growth [57]. These findings place HDAC3 within a broader system of AR/ARE enhancer control and support the concept that HOXB13-HDAC3 interactions may influence metabolic and lineage-associated transcriptional states through context-specific chromatin repression.

HOXB13 interacts with HDAC3 and recruits it to lipogenic regulatory regions [50]. This recruitment maintains low enhancer acetylation and suppresses de novo lipogenesis. When HOXB13 is lost or functionally impaired, HDAC3 occupancy decreases, enhancer acetylation increases, and lipogenic genes become activated [50]. Thus, HOXB13 can function as a chromatin-level metabolic repressor.

This mechanism introduces the concept of cofactor balance. In HOXB13-intact states, HDAC3-mediated repression may restrain lipogenic enhancers. In HOXB13-deficient states, this repressive balance may be lost, allowing p300/CBP-mediated enhancer activation and H3K27ac accumulation [51]. Because p300 and CBP are major histone acetyltransferases that activate enhancers and super-enhancers [58], HOXB13 may regulate metabolism by controlling the balance between repressive and activating chromatin machinery.

HOXB13 itself can also be modified. Acetylation of HOXB13 at lysine 13 by CBP/p300 has been linked to clinically significant prostate cancer and CRPC-associated super-enhancer programs [52]. This suggests that HOXB13 activity can be redirected by acetylation and may support distinct enhancer states in advanced disease. Phosphorylation represents another regulatory layer. mTOR-mediated hierarchical phosphorylation of HOXB13 has been reported to influence HOXB13 activity and oncogenic function. Mechanistically, mTOR phosphorylates HOXB13 at T8 and T41, which primes subsequent S31 phosphorylation, promotes SKP2-dependent proteasomal

degradation, and paradoxically enhances HOXB13 oncogenic activity [53]. Together, these findings indicate that HOXB13 function cannot be inferred solely from expression level.

A more refined model is that prostate cancer cells contain distinct HOXB13 functional states: HOXB13-AR-cooperative, HOXB13-HDAC3-repressive, HOXB13-acetylated-super-enhancer-associated, HOXB13-mutant-lipogenic, and potentially HOXB13-kinase-modified-metabolically rewired. Defining these states may be more informative than simply classifying tumors as HOXB13-high or HOXB13-low.

5. HOXB13–HDAC3 Axis in Lipid Metabolic Reprogramming and Metastasis

Lipid metabolism is a central adaptive program in prostate cancer and is closely linked to androgen receptor signaling, tumor progression, and therapy resistance. Prostate cancer often displays prominent lipid and mitochondrial metabolism, with androgen receptor signaling promoting fatty acid synthesis, cholesterol biosynthesis, lipid uptake, and oxidative metabolism [22-33]. De novo lipogenesis, mediated by regulators such as FASN, ACC, ACLY, SREBP transcription factors, and SCD, supports membrane production, signaling lipid generation, and stress adaptation [28-35]. In advanced or therapy-resistant disease, additional lipid programs, including cholesterol homeostasis, lipid droplet storage, fatty acid elongation, fatty acid oxidation, and mevalonate pathway activity, can further support tumor growth and resistance to androgen receptor pathway inhibition [27-36, 59-69]. These studies provide the metabolic context for HOXB13 biology: lipid metabolism is not only enzyme-driven, but also controlled by lineage-associated transcriptional and chromatin-regulatory mechanisms.

Within this framework, the discovery that HOXB13 suppresses de novo lipogenesis through HDAC3-mediated epigenetic repression substantially expanded the conceptual understanding of HOXB13 function in prostate cancer [50]. Lu and colleagues showed that HOXB13 interacts with HDAC3 and recruits it to lipogenic regulatory regions, maintaining low enhancer acetylation and restraining lipogenic gene expression. When HOXB13 is depleted, lost, or functionally impaired, HDAC3 recruitment decreases, enhancer acetylation increases, and lipogenic programs become activated [50]. Functionally, HOXB13 loss or the hereditary prostate cancer-associated G84E mutation increases lipid accumulation, tumor cell motility, and xenograft metastasis, whereas FASN inhibition attenuates HOXB13-loss-associated metastatic phenotypes [50]. HOXB13 loss may also shift enhancer regulation from HDAC3-mediated repression toward p300/CBP-dependent activation and increased H3K27ac, leading to metabolic and metastatic reprogramming [51]. Thus, the HOXB13-HDAC3 axis provides a direct mechanistic link between prostate lineage identity, chromatin repression, lipid metabolic control, and metastasis, and suggests that HOXB13-low, HOXB13-mutant, or functionally impaired tumors may represent lipogenic-dependent states vulnerable to targeting FASN, SREBP-driven pathways, p300/CBP activity, or related metabolic enhancer programs.

6. Beyond Lipogenesis: HOXB13, Glycolysis, Hypoxia, and Broader Metabolic Plasticity

Although HOXB13-dependent repression of lipogenesis is well supported, the relationship between HOXB13, glycolysis, and hypoxia remains less defined. This distinction is important because aggressive prostate cancer can acquire glycolytic, hypoxic, mitochondrial, and redox-adaptive programs during CRPC progression, metastasis, and neuroendocrine transformation [22-27, 70-76]. However, current evidence more strongly supports HOXB13 as a regulator of lipogenic enhancer repression than as a direct regulator of glycolytic transcription [50].

Several therapy-resistant metabolic pathways provide context for this unresolved HOXB13 question. Glycolysis- and hypoxia-associated regulators, including HIF1α, LDHA, PGK1, ENO1, ALDOA/ALDOC, and PFKFB3, support survival under oxygen limitation or therapeutic stress [70-76]. KDM5B-driven glucose metabolic reprogramming has been linked to enzalutamide resistance through a lactate/hnRNPA1 lactylation/AR-V7 axis, while lactate, AZGP1 loss, TXNIP regulation, NXPH4/ALDH1L2 signaling, tricarboxylic acid cycle dysregulation, and redox homeostasis have each been implicated in prostate cancer progression or therapy resistance [77-85]. These pathways should be viewed as part of the metabolic landscape in which HOXB13 functional states may operate, rather than as established direct HOXB13 targets.

Several non-mutually exclusive models may explain how HOXB13 could relate to glycolytic-hypoxic adaptation. HOXB13 may indirectly restrain stress-associated metabolic programs by maintaining

Table 1. Major HOXB13-Associated Regulatory Mechanisms and Implications in Prostate Cancer

Mechanism	Molecular players	Disease context	Biological output	Therapeutic implication
AR cistrome organization	HOXB13, AR, FOXA1, GATA2	Primary PCa/CRPC	Lineage transcription	AR-targeted therapy
AR-V7 regulation	HOXB13, AR-V7	CRPC	Ligand-independent AR signaling	AR variant/ adaptive targeting
Lipogenesis repression	HOXB13, HDAC3	HOXB13-intact PCa	Low lipogenic enhancer activity	Biomarker of metabolic state
Lipogenic activation	HOXB13 loss/G84E, p300/CBP	Metastatic/ metabolic PCa	FASN/SREBP/lipid droplets	FASN or p300/ CBP inhibition
Acetylated HOXB13/ super-enhancer state	Ac-HOXB13, CBP/p300, BRD9	CRPC	Enhancer-associated transcription	Epigenetic therapy
Post-translational regulation	mTOR; potential PLK1-associated kinase signaling	Advanced PCa	Altered HOXB13 function	Future kinase-based strategies
Direct HOXB13 targeting	SCORT-Cas13d-gHoxB13	Metastatic PCa models	HOXB13 suppression	Experimental HOXB13-targeted therapy

androgen receptor/luminal identity; altered HOXB13 activity may redirect chromatin binding or cofactor recruitment toward stress-response loci; post-translational modifications may influence whether HOXB13 favors lineage maintenance, lipogenic repression, or metabolic adaptation; and HOXB13 loss may create permissive chromatin states that allow hypoxia- or plasticity-associated transcription factors to engage metabolic enhancers. Future RNA-seq, ATAC-seq, CUT&RUN/ChIP-seq, metabolomics, lipidomics, isotope tracing, and functional metabolic assays will be needed to determine whether HOXB13 functional states correspond to lipid-dominant, glycolytic-hypoxic, oxidative, or hybrid metabolic phenotypes.

7. CRPC, Therapy Resistance, and the Need for HOXB13 Functional-State Models

CRPC is not a single disease state. It includes androgen receptor-driven tumors with persistent androgen receptor activity, androgen receptor-variant-driven tumors, tumors with altered enhancer landscapes, and androgen receptor-indifferent tumors with lineage plasticity [7-15, 19-21, 86-93]. Integrative genomic studies have revealed recurrent alterations in AR, PI3K pathway components, DNA repair genes, TP53, RB1, and chromatin regulators in advanced prostate cancer [6-13, 86-93]. However, transcriptional state and enhancer organization remain critical determinants of therapeutic response.

HOXB13 may contribute to CRPC through several mechanisms. In androgen receptor-driven CRPC, HOXB13 can help maintain androgen receptor transcriptional programs and govern AR-V7 cistromes [49]. In acetylated-HOXB13 states, HOXB13 may participate in super-enhancer-associated transcription and define therapeutic vulnerabilities [52]. In HOXB13-low or mutant states, loss of HDAC3-mediated repression may activate lipogenic programs that support metastasis [50]. Thus, HOXB13 may have distinct functions across CRPC subtypes.

Recent circulating tumor cell studies further support the clinical relevance of HOXB13 as a marker of prostate-lineage and AR-associated disease states in advanced prostate cancer. Promoter analysis of plasma microRNA signatures in prostate cancer highlighted enrichment of transcription factor binding sites associated with developmental regulators, including HOX and SOX family members such as HOXB13 and SOX10, as well as cancer-related genes such as BRCA1[94]. Importantly, HOXB13 has also been detected at high levels in circulating tumor cells from men with metastatic castration-resistant prostate cancer treated with androgen receptor pathway inhibitors. In the PROPHECY trial cohort, higher CTC HOXB13 RNA expression was associated with AR-dependent CTC biomarkers and adverse outcomes in men receiving abiraterone or enzalutamide [95]. These observations suggest that HOXB13 may have translational relevance beyond tissue-based prostate lineage identity, potentially serving as a blood-based indicator of persistent AR-lineage programs and poor response to potent AR inhibition.

However, whether elevated CTC HOXB13 reflects therapy-resistant AR dependence, tumor burden, lineage state, or a distinct HOXB13-driven functional program remains to be clarified.

This complexity supports a functional-state model in which HOXB13 activity is defined by chromatin occupancy, cofactor engagement, post-translational modification, and disease context rather than by expression level alone. Key determinants include binding to androgen receptor-associated enhancers, recruitment of HDAC3 to lipogenic loci, acetylation-linked association with super-enhancers, phosphorylation-dependent regulation by oncogenic signaling pathways, mutation or degradation status, and cooperation with factors such as FOXA1, GATA2, AR-V7, p300/CBP, and HDAC3.

A functional-state model could explain why HOXB13 may be associated with both prostate lineage maintenance and aggressive disease behavior. In one state, HOXB13 maintains luminal identity and androgen receptor-dependent differentiation. In another, HOXB13 supports androgen receptor adaptation in CRPC. In another, HOXB13 loss permits lipogenic and metastatic reprogramming. These states are not mutually exclusive across disease evolution; a tumor may transition between them under therapy pressure.

8. HOXB13, Lineage Plasticity, and Neuroendocrine Progression

Lineage plasticity is a major mechanism by which prostate cancer escapes androgen receptor pathway inhibition. Under pressure from androgen deprivation therapy, enzalutamide, or abiraterone acetate, some tumors do not simply restore androgen receptor activity; instead, they reduce androgen receptor dependence and acquire alternative lineage states [96, 97].

In classical prostate adenocarcinoma, tumor cells are largely driven by luminal prostate identity and androgen receptor signaling. During therapy resistance, tumors may lose prostate differentiation programs and acquire basal-like, stem-like, or neuroendocrine-like features, accompanied by changes in transcriptional networks, chromatin states, and metabolic dependencies [14, 15, 19-21, 96, 98-105].

Treatment-emergent neuroendocrine prostate cancer represents an aggressive endpoint of this process and is characterized by reduced androgen receptor dependence, loss of luminal identity, and acquisition of neuroendocrine markers such as chromogranin A, synaptophysin, neuron-specific enolase, and CD56 [14, 15, 104, 106].

Mechanistic studies show that lineage plasticity is driven by genetic lesions, transcription factors, epigenetic regulators, inflammatory signaling, and therapy-imposed selective pressure. Rb1 and Trp53 cooperate to suppress lineage plasticity, metastasis, and antiandrogen resistance, while TP53/RB1 loss can enable SOX2-associated plasticity [92, 93]. MYCN, EZH2, BRN2, and JAK/STAT signaling further contribute to neuroendocrine or lineage-plastic states [98-104]. These pathways provide the broader context in which HOXB13-linked prostate identity may be lost, retained, or rewired.

HOXB13 expression is generally retained in prostate adenocarcinoma and many androgen receptor-driven states, but it may decrease in neuroendocrine-like contexts. Cheng and colleagues reported that neuroendocrine prostate cancer exhibits a distinctive non-prostatic HOX code represented by loss of HOXB13 expression [105]. However, this relationship is not absolute. Ersoy-Fazlioglu and colleagues reported that HOXB13 is highly expressed in primary prostate cancer, adenocarcinoma CRPC, and AR-positive treatment-emergent NEPC, while some AR-negative treatment-emergent NEPC and AR-negative CRPC tumors also retain HOXB13 expression [107]. Thus, HOXB13 loss may accompany loss of prostate identity in some tumors, whereas retained HOXB13 may support distinct AR-dependent or AR-independent regulatory programs in others.

Therefore, HOXB13 should not be interpreted only as a passive lineage marker. When HOXB13 maintains prostate enhancer architecture and androgen receptor-associated transcription, it may reinforce luminal identity. Conversely, loss or functional impairment of HOXB13 may destabilize prostate-lineage enhancers, reduce androgen receptor-linked differentiation programs, and create permissive chromatin states for alternative lineage factors. HOXB13-dependent metabolic regulation may also contribute to this process, because HOXB13 loss activates lipogenic programs through loss of HDAC3-mediated repression and may support invasion, metastasis, and survival under therapy [50].

9. Post-Translational Regulation of HOXB13: Acetylation, Phosphorylation, and Emerging Kinase Control

A major limitation of the current field is that HOXB13 is often evaluated primarily by expression

level. Yet transcription factor activity is frequently controlled by post-translational modifications, including phosphorylation, acetylation, ubiquitination, SUMOylation, and methylation. These modifications can regulate protein stability, DNA binding, cofactor recruitment, chromatin occupancy, and transcriptional specificity.

Acetylation of HOXB13 at lysine 13 by CBP/p300 has been linked to CRPC-associated super-enhancer biology and clinically significant prostate cancer [52]. This suggests that acetylated HOXB13 may represent a distinct functional state with therapeutic implications. In this context, HOXB13 may contribute to enhancer-driven transcriptional programs that support CRPC progression.

The clinical relevance of acetylated HOXB13 may extend beyond enhancer activation and CRPC progression. Recent reviews of prostate cancer immune suppression have highlighted HOXB13 K13 acetylation as part of a broader epigenetic program associated with castration resistance, chromatin remodeling, and therapy resistance. In this model, CBP/p300-mediated acetylation of HOXB13 creates a modified transcription factor state that can be recognized by bromodomain-containing chromatin readers, including BRD9, thereby promoting transcriptionally active chromatin at selected tumor-associated super-enhancers. Although the immune consequences of HOXB13 acetylation require further mechanistic validation, these observations support the broader concept that HOXB13 post-translational modifications may reshape lineage, chromatin, and tumor-microenvironmental states in advanced prostate cancer [108].

Kinase-dependent HOXB13 regulation should also be considered within the broader signaling landscape of advanced prostate cancer. AR signaling and the PI3K/AKT/mTOR pathway engage in reciprocal crosstalk, and compensatory activation of one pathway can occur when the other is therapeutically inhibited [86, 109]. This reciprocal interaction has provided a rationale for combined targeting of AR and PI3K/AKT/mTOR signaling in prostate cancer, although clinical benefit has been limited by toxicity, pathway complexity, and the need for predictive biomarkers [86, 109]. Growth factor- and nutrient-sensing pathways may therefore influence prostate lineage transcriptional programs through direct or indirect regulation of lineage-associated transcription factors.

Phosphorylation provides a direct example of this concept. mTOR-mediated hierarchical phosphorylation of HOXB13 has been reported to influence HOXB13 activity and oncogenic function [53]. This finding indicates that HOXB13 can be regulated by upstream kinase signaling and suggests that kinase-dependent modification of HOXB13 may represent a broader mechanism by which prostate cancer cells remodel lineage transcription factor activity during progression and therapy resistance.

A mature functional-state model of HOXB13 should therefore include not only expression and mutation, but also post-translational regulation. Potential HOXB13 states may include HOXB13-AR-cooperative, HOXB13-HDAC3-repressive, HOXB13-acetylated-super-enhancer-associated, HOXB13-mTOR-phosphorylated-oncogenic, HOXB13-low-lipogenic, and potentially HOXB13-kinase-modified-metabolically rewired. Defining these states may reveal how extracellular signals, cell-cycle kinases, metabolic stress, and therapy pressure alter HOXB13 output during prostate cancer progression.

10. Therapeutic Implications

The HOXB13-centered model has several therapeutic implications. First, HOXB13-low or HOXB13-mutant tumors may be vulnerable to lipid metabolism inhibitors. The ability of FASN inhibition to mitigate HOXB13-loss-induced motility and metastasis supports this concept [50]. More broadly, FASN, SREBP signaling, cholesterol metabolism, lipid desaturation, and lipid droplet biology represent potential vulnerabilities in lipid-rewired prostate cancer [28-36, 59-69].

Second, HOXB13-deficient tumors may be vulnerable to enhancer-targeted therapies. Loss of HOXB13-HDAC3 repression can shift enhancer balance toward p300/CBP-mediated activation [51]. Therefore, p300/CBP inhibitors may counteract lipogenic enhancer activation in HOXB13-low contexts. This strategy is conceptually distinct from general chromatin inhibition because it is tied to a defined transcription factor state.

Third, acetylated HOXB13-associated super-enhancer programs may define therapeutic vulnerabilities in CRPC [52]. This suggests that HOXB13 modifications could function as biomarkers for selecting enhancer-targeted or pathway-specific therapies.

An emerging therapeutic direction is direct targeting of HOXB13 itself. Although transcription factors have historically been difficult to drug, RNA-targeting and nanodelivery technologies may create new opportunities to suppress lineage-defining oncogenic

transcription factors. Cui and colleagues developed a SCORT-Cas13d lipid nanoparticle nanotherapy designed to deliver Cas13d mRNA and guide RNAs targeting HoxB13 to metastatic prostate tumors *in vivo* [110]. In HoxB13-driven prostate cancer liver metastasis models, systemic SCORT-Cas13d-gHoxB13 treatment reduced HoxB13 expression, decreased metastatic burden, and extended mouse survival without major toxicity in evaluated organs. These findings provide preclinical proof-of-concept that HOXB13 may be therapeutically targetable, although delivery efficiency, durability, safety, tumor specificity, and disease-state dependence require further study [110].

Fourth, post-translational regulators of HOXB13 may represent upstream therapeutic targets. Acetyltransferases, deacetylases, ubiquitin ligases, metabolic enzymes, kinases, and chromatin modifiers can alter transcription factor activity by regulating protein stability, cofactor recruitment, chromatin occupancy, and transcriptional output [52, 53].

Finally, HOXB13 functional states may guide combination therapy. Androgen receptor pathway inhibitors could be combined with lipid metabolism inhibitors, p300/CBP inhibitors, HDAC-related strategies, kinase inhibitors, direct HOXB13-targeting strategies, or glycolysis/hypoxia-targeted therapies depending on tumor state. For example, androgen receptor-driven/HOXB13-high tumors may require androgen receptor-focused strategies, whereas HOXB13-low/lipogenic tumors may require metabolic or enhancer-targeted therapies. Lineage-plastic tumors may require combinations targeting epigenetic regulators, inflammatory signaling, and metabolic adaptation.

The major translational challenge is biomarker development. HOXB13 expression alone may be insufficient. Better biomarkers may include HOXB13 mutation status, HOXB13 chromatin binding, HDAC3 recruitment, enhancer acetylation, acetylated-HOXB13, phosphorylated-HOXB13, lipogenic gene signatures, glycolytic-hypoxic signatures, and metabolic imaging or metabolomic readouts.

11. Future Directions

First, the determinants of HOXB13 functional state require systematic definition. Expression, mutation, chromatin accessibility, cofactor levels, androgen receptor status, phosphorylation, acetylation, and degradation may all contribute. Mapping these variables across localized prostate cancer, CRPC, NEPC, and treatment-resistant models will be essential.

Second, the potential regulation of glycolytic and hypoxia-associated enhancers by HOXB13 remains an important unresolved area. Direct chromatin profiling of HOXB13, HDAC3, p300/CBP, H3K27ac, and H3K27me3 at glycolytic and hypoxic loci would help determine whether HOXB13 functional states extend beyond lipid metabolism.

Third, HOXB13 variants should be compared functionally. G84E is the best-studied hereditary risk variant, but other HOXB13 variants may have distinct effects on DNA binding, cofactor recruitment, protein stability, or metabolic regulation.

Fourth, the interaction between HOXB13 and lineage-plasticity drivers should be defined. Integrating HOXB13 profiling with TP53/RB1 loss, SOX2, MYCN, EZH2, BRN2, and JAK/STAT models could clarify whether HOXB13 loss is a cause, consequence, or modifier of lineage transition.

Fifth, kinase-dependent regulation of HOXB13 activity should be investigated. Published studies support acetylation- and phosphorylation-dependent regulation of HOXB13 [52, 53]. Future studies should determine whether additional kinases like PLK1 regulate HOXB13 stability, chromatin binding, cofactor selection, degradation, or metabolic output. This priority is particularly important because kinase signaling may provide a rapid mechanism for rewiring transcription factor activity under therapy pressure.

Sixth, HOXB13 functional states should be tested as predictors of therapy response. Patient-derived organoids, xenografts, genetically engineered mouse models, and clinical datasets should be used to determine whether HOXB13-low/lipogenic, acetylated-HOXB13/super-enhancer, phosphorylated-HOXB13/kinase-regulated, or HOXB13-lineage-plastic states predict sensitivity to FASN inhibitors, p300/CBP inhibitors, AR inhibitors, kinase inhibitors, direct HOXB13-targeting strategies, or rational combination therapies. Finally, HOXB13 should be studied using integrated multi-omics. RNA-seq alone is insufficient. The field needs combined chromatin profiling, proteomics, metabolomics, phosphoproteomics, lipidomics, isotope tracing, and functional assays to understand how HOXB13 rewires transcription and metabolism during progression.

12. Conclusion

HOXB13 is a prostate lineage transcription factor that sits at the intersection of androgen receptor signaling, chromatin regulation, metabolic state, and therapy-induced plasticity. Its function extends beyond prostate identity. HOXB13 helps organize tumor-specific androgen receptor cistromes, governs AR-V7 transcriptional programs in CRPC, recruits HDAC3 to suppress lipogenic enhancers, and may be redirected by post-translational modifications and cofactor switching. Loss, mutation, or functional alteration of HOXB13 can activate lipid metabolism, promote metastatic phenotypes, and potentially contribute to therapy resistance.

A mature model of HOXB13 biology must therefore move beyond expression level. HOXB13 should be understood as a dynamic chromatin-metabolic platform whose activity depends on genomic context, androgen receptor state, cofactor recruitment, mutation status, and post-translational regulation. Acetylation and phosphorylation studies already support the concept that HOXB13 functional states are signal-dependent. Additional kinase pathways represent important candidates for future investigation, particularly in the context of advanced prostate cancer, metabolic plasticity, and therapy resistance.

Defining HOXB13 functional states may reveal new biomarkers and therapeutic vulnerabilities in CRPC, NEPC, and treatment-resistant prostate cancer.

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Declaration of interests:

The authors declare no competing interests.

References

1. Huggins C, Hodges CV: **Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate**. *CA: A Cancer Journal for Clinicians* 1972, **22**(4):232–240. doi:https://doi.org/10.3322/canjclin.22.4.232:
2. Attard G, Parker C, Eeles RA, Schröder F, Tomlins SA, Tannock I, Drake CG, de Bono JS: **Prostate cancer**. *The Lancet* 2016, **387**(10013):70–82. doi:10.1016/S0140-6736(14)61947-4:
3. Watson PA, Arora VK, Sawyers CL: **Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer**. *Nature Reviews Cancer* 2015, **15**(12):701–711. doi:10.1038/nrc4016:
4. Culig Z, Santer FR: **Androgen receptor signaling in prostate cancer**. *Cancer and Metastasis Reviews* 2014, **33**(2):413–427. doi:10.1007/s10555-013-9474-0:
5. Dai C, Heemers H, Sharifi N: **Androgen signaling in prostate cancer**. *Cold Spring Harbor perspectives in medicine* 2017, **7**(9):a030452.
6. Cancer Genome Atlas Research N: **The Molecular Taxonomy of Primary Prostate Cancer**. *Cell* 2015, **163**:4.
7. Robinson D, Van Allen EM, Wu Y-M, Schultz N, Lonigro RJ, Mosquera J-M, Montgomery B, Taplin M-E, Pritchard CC, Attard G: **Integrative clinical genomics of advanced prostate cancer**. *Cell* 2015, **161**(5):1215–1228.
8. Grasso CS, Wu Y-M, Robinson DR, Cao X, Dhanasekaran SM, Khan AP, Quist MJ, Jing X, Lonigro RJ, Brenner JC: **The mutational landscape of lethal castration-resistant prostate cancer**. *Nature* 2012, **487**(7406):239–243.
9. Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, Cieslik M, Benelli M, Robinson D, Van Allen EM: **Genomic correlates of clinical outcome in advanced prostate cancer**. *Proceedings of the National Academy of Sciences* 2019, **116**(23):11428–11436.
10. Armenia J, Wankowicz SAM, Liu D, Gao J, Kundra R, Reznik E, Chatila WK, Chakravarty D, Han GC, Coleman I: **The long tail of oncogenic drivers in prostate cancer**. *Nature genetics* 2018, **50**(5):645–651.
11. Quigley DA, Dang HX, Zhao SG, Lloyd P, Aggarwal R, Alumkal JJ, Foye A, Kothari V, Perry MD, Bailey AM: **Genomic hallmarks and structural variation in metastatic prostate cancer**. *Cell* 2018, **174**(3):758–769.
12. Baca SC, Prandi D, Lawrence MS, Mosquera JM, Romanel A, Drier Y, Park K, Kitabayashi N, Mac-

Donald TY, Ghandi M: **Punctuated evolution of prostate cancer genomes**. *Cell* 2013, **153**(3):666–677.
13. Viswanathan SR, Ha G, Hoff AM, Wala JA, Carrot-Zhang J, Whelan CW, Haradhvala NJ, Freeman SS, Reed SC, Rhoades J: **Structural alterations driving castration-resistant prostate cancer revealed by linked-read genome sequencing**. *Cell* 2018, **174**(2):433–447.
14. Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyrta J, Marotz C, Giannopoulou E, Chakravarthi BVSK, Varambally S: **Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer**. *Nature medicine* 2016, **22**(3):298–305.
15. Aggarwal R, Huang J, Alumkal JJ, Zhang L, Feng FY, Thomas GV, Weinstein AS, Friedl V, Zhang C, Witte ON: **Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study**. *Journal of Clinical Oncology* 2018, **36**(24):2492–2503.
16. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S: **Enzalutamide in metastatic prostate cancer before chemotherapy**. *New England Journal of Medicine* 2014, **371**(5):424–433.
17. Ryan CJ, Smith MR, De Bono JS, Molina A, Logothetis CJ, De Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S: **Abiraterone in metastatic prostate cancer without previous chemotherapy**. *New England Journal of Medicine* 2013, **368**(2):138–148.
18. De Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman Jr OB, Saad F: **Abiraterone and increased survival in metastatic prostate cancer**. *New England Journal of Medicine* 2011, **364**(21):1995–2005.
19. Bluemn EG, Coleman IM, Lucas JM, Coleman RT, Hernandez-Lopez S, Tharakan R, Bianchi-Frias D, Dumpit RF, Kaipainen A, Corella AN: **Androgen receptor pathway-independent prostate cancer is sustained through FGF signaling**. *Cancer cell* 2017, **32**(4):474–489.
20. Labrecque MP, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, Nguyen HM, Yang YC, da Costa RMG, Kaipainen A: **Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer**. *The Journal of clinical investigation* 2019, **129**(10):4492–4505.
21. Aparicio AM, Shen L, Tapia ELN, Lu J-F, Chen H-C, Zhang J, Wu G, Wang X, Troncoso P, Corn P: **Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers**. *Clinical cancer research* 2016, **22**(6):1520–1530.
22. Costello LCa, Franklin RB: **The intermediary metabolism of the prostate: a key to understanding the pathogenesis and progression of prostate malignancy**. *Oncology* 2000, **59**(4):269–282.
23. Costello LC, Franklin RB: **A comprehensive review of the role of zinc in normal prostate function and metabolism; and its implications in prostate cancer**. *Archives of biochemistry and biophysics* 2016, **611**:100–112.
24. Bader DA, McGuire SE: **Tumour metabolism and its unique properties in prostate adenocarcinoma**. *Nature Reviews Urology* 2020, **17**(4):214–231.
25. Ahmad F, Cherukuri MK, Choyke PL: **Metabolic reprogramming in prostate cancer**. *British journal of cancer* 2021, **125**(9):1185–1196.
26. Pujana-Vaquerizo M, Bozal-Basterra L, Carracedo A: **Metabolic adaptations in prostate cancer**. *British Journal of Cancer* 2024, **131**(8):1250–1262.
27. Uo T, Sprenger CC, Plymate SR: **Androgen receptor signaling and metabolic and cellular plasticity during progression to castration resistant prostate cancer**. *Frontiers in oncology* 2020, **10**:580617.
28. Massie CE, Lynch A, Ramos-Montoya A, Boren J, Stark R, Fazli L, Warren A, Scott H, Madhu B, Sharma N: **The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis**. *The EMBO journal* 2011, **30**(13):2719–2733.
29. Swinnen JV, Esquenet M, Goossens K, Heyns W, Verhoeven G: **Androgens stimulate fatty acid synthease in the human prostate cancer cell line LNCaP**. *Cancer research* 1997, **57**(6):1086–1090.
30. Zadra G, Photopoulos C, Loda M: **The fat side of prostate cancer**. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids* 2013, **1831**(10):1518–1532.
31. Zadra G, Ribeiro CF, Chetta P, Ho Y, Cacciatore S, Gao X, Syamala S, Bango C, Photopoulos C, Huang Y: **Inhibition of de novo lipogenesis targets androgen receptor signaling in castration-resistant prostate cancer**. *Proceedings of the*

National Academy of Sciences 2019, **116**(2):631–640.

32. Migita T, Ruiz S, Fornari A, Fiorentino M, Priolo C, Zadra G, Inazuka F, Grisanzio C, Palescandolo E, Shin E: **Fatty acid synthase: a metabolic enzyme and candidate oncogene in prostate cancer**. *Journal of the National Cancer Institute* 2009, **101**(7):519–532.
33. Huang W-C, Li X, Liu J, Lin J, Chung LWK: **Activation of androgen receptor, lipogenesis, and oxidative stress converged by SREBP-1 is responsible for regulating growth and progression of prostate cancer cells**. *Molecular Cancer Research* 2012, **10**(1):133–142.
34. Yue S, Li J, Lee S-Y, Lee HJ, Shao T, Song B, Cheng L, Masterson TA, Liu X, Ratliff TL: **Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness**. *Cell metabolism* 2014, **19**(3):393–406.
35. Freeman MR, Solomon KR: **Cholesterol and prostate cancer**. *Journal of cellular biochemistry* 2004, **91**(1):54–69.
36. Li X, Chen Y-T, Hu P, Huang W-C: **Fatostatin displays high antitumor activity in prostate cancer by blocking SREBP-regulated metabolic pathways and androgen receptor signaling**. *Molecular cancer therapeutics* 2014, **13**(4):855–866.
37. Vander Heiden MG, DeBerardinis RJ: **Understanding the Intersections between Metabolism and Cancer Biology**. *Cell* 2017, **168**(4):657–669. doi:https://doi.org/10.1016/j.cell.2016.12.039:
38. McGinnis W, Krumlauf R: **Homeobox genes and axial patterning**. *Cell* 1992, **68**(2):283–302. doi:https://doi.org/10.1016/0092-8674(92)90471-N:
39. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, Wiley KE, Isaacs SD, Johng D, Wang Y: **Germline mutations in HOXB13 and prostate-cancer risk**. *New England Journal of Medicine* 2012, **366**(2):141–149.
40. Chen Z, Greenwood C, Isaacs WB, Foulkes WD, Sun J, Zheng SL, Condreay LD, Xu J: **The G84E mutation of HOXB13 is associated with increased risk for prostate cancer: results from the REDUCE trial**. *Carcinogenesis* 2013, **34**(6):1260–1264.
41. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, Dadaev T, Tymrakiewicz M, Saunders EJ, Jones M, Jugurnauth-Little S, Govindasami K, Guy M: **Prevalence of theHOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes**. *Annals of oncology* 2015, **26**(4):756–761.
42. Patel RA, Sayar E, Coleman I, Roudier MP, Hanratty B, Low JY, Jaiswal N, Ajkunic A, Dumpit R, Ercan C: **Characterization of HOXB13 expression patterns in localized and metastatic castration-resistant prostate cancer**. *The Journal of pathology* 2024, **262**(1):105–120.
43. Jung C, Kim R-S, Zhang H-J, Lee S-J, Jeng M-H: **HOXB13 Induces Growth Suppression of Prostate Cancer Cells as a Repressor of Hormone-Activated Androgen Receptor Signaling**. *Cancer Research* 2004, **64**(24):9185–9192. doi:10.1158/0008-5472.CAN-04-1330:
44. Norris JD, Chang C-Y, Wittmann BM, Kunder RS, Cui H, Fan D, Joseph JD, McDonnell DP: **The Homeodomain Protein HOXB13 Regulates the Cellular Response to Androgens**. *Molecular Cell* 2009, **36**(3):405–416. doi:10.1016/j.molcel.2009.10.020:
45. Pomerantz MM, Li F, Takeda DY, Lenci R, Chonkar A, Chabot M, Cejas P, Vazquez F, Cook J, Shivdasani RA *et al*: **The androgen receptor cistrome is extensively reprogrammed in human prostate tumorigenesis**. *Nature Genetics* 2015, **47**(11):1346–1351. doi:10.1038/ng.3419:
46. Hankey W, Chen Z, Wang Q: **Shaping Chromatin States in Prostate Cancer by Pioneer Transcription Factors**. *Cancer Research* 2020, **80**(12):2427–2436. doi:10.1158/0008-5472.CAN-19-3447:
47. Sahu B, Laakso M, Ovaska K, Mirtti T, Lundin J, Rannikko A, Sankila A, Turunen JP, Lundin M, Konsti J *et al*: **Dual role of FoxA1 in androgen receptor binding to chromatin, androgen signalling and prostate cancer**. *The EMBO Journal* 2011, **30**(19):3962–3976. doi:10.1038/emboj.2011.328:
48. Jin H-J, Zhao JC, Wu L, Kim J, Yu J: **Cooperativity and equilibrium with FOXA1 define the androgen receptor transcriptional program**. *Nature Communications* 2014, **5**(1):3972. doi:10.1038/ncomms4972:
49. Chen Z, Wu D, Thomas-Ahner JM, Lu C, Zhao P, Zhang Q, Geraghty C, Yan PS, Hankey W, Sunkel B *et al*: **Diverse AR-V7 cistromes in castra-**

tion-resistant prostate cancer are governed by HoxB13. *Proceedings of the National Academy of Sciences* 2018, **115**(26):6810–6815. doi:10.1073/pnas.1718811115:

50. Lu X, Fong K-w, Gritsina G, Wang F, Baca SC, Brea LT, Berchuck JE, Spisak S, Ross J, Morrissey C *et al*: **HOXB13 suppresses de novo lipogenesis through HDAC3-mediated epigenetic reprogramming in prostate cancer**. *Nature Genetics* 2022, **54**(5):670–683. doi:10.1038/s41588-022-01045-8:
51. Lu X, Peng L, Chu Q, Ye S, Liu M, Hussain M, Bilen MA, Harik LR, Melamed J, Zhao JC *et al*: **Targeting p300 and CBP abolishes HOXB13-loss-induced lipogenesis and tumor metastasis**. *JCI Insight* 2025, **10**(22). doi:10.1172/jci.insight.195743:
52. Nguyen DT, Yang W, Renganathan A, Weimholt C, Angappulige DH, Nguyen T, Sprung RW, Andriole GL, Kim EH, Mahajan NP *et al*: **Acetylated HOXB13 Regulated Super Enhancer Genes Define Therapeutic Vulnerabilities of Castration-Resistant Prostate Cancer**. *Clinical Cancer Research* 2022, **28**(18):4131–4145. doi:10.1158/1078-0432.CCR-21-3603:
53. Chen Y, Dufour CR, Han L, Li T, Xia H, Giguère V: **Hierarchical Phosphorylation of HOXB13 by mTOR Dictates Its Activity and Oncogenic Function in Prostate Cancer**. *Molecular Cancer Research* 2023, **21**(10):1050–1063. doi:10.1158/1541-7786.MCR-23-0086:
54. Brechka H, Bhanvadia RR, VanOpstall C, Vander Griend DJ: **HOXB13 mutations and binding partners in prostate development and cancer: Function, clinical significance, and future directions**. *Genes & Diseases* 2017, **4**(2):75–87. doi:https://doi.org/10.1016/j.gendis.2017.01.003:
55. Bhanvadia RR, VanOpstall C, Brechka H, Barashi NS, Gillard M, McAuley EM, Vasquez JM, Paner G, Chan W-C, Andrade J *et al*: **MEIS1 and MEIS2 Expression and Prostate Cancer Progression: A Role For HOXB13 Binding Partners in Metastatic Disease**. *Clinical Cancer Research* 2018, **24**(15):3668–3680. doi:10.1158/1078-0432.CCR-17-3673:
56. Kim EH, Cao D, Mahajan NP, Andriole GL, Mahajan K: **ACK1–AR and AR–HOXB13 signaling axes: epigenetic regulation of lethal prostate cancers**. *NAR Cancer* 2020, **2**(3):zcaa018. doi:10.1093/narcan/zcaa018:
57. Chen X, Augello MA, Liu D, Lin K, Hakansson A, Sjöström M, Khani F, Deonarine LD, Liu Y, Travascio-Green J *et al*: **Canonical androgen response element motifs are tumor suppressive regulatory elements in the prostate**. *Nature Communications* 2024, **15**(1):10675. doi:10.1038/s41467-024-53734-z:
58. Liu J, Wang X, He D, Maasoumyhaghighi H, Nouri M, Wu M, Peng J, Rao X, Wang R, Wu S *et al*: **Therapeutic targeting of the p300/CBP bromodomain enhances the efficacy of immune checkpoint blockade therapy**. *Oncogene* 2025, **44**(28):2386–2395. doi:10.1038/s41388-025-03417-w:
59. Yang N, Yang Y, Huang Z, Chen H-W: **Deregulation of Cholesterol Homeostasis by a Nuclear Hormone Receptor Crosstalk in Advanced Prostate Cancer**. In: *Cancers*. vol. 14; 2022: 3110.
60. Dairo O, DePaula Oliveira L, Schaffer E, Vidotto T, Mendes AA, Lu J, Huynh SV, Hicks J, Sowalsky AG, De Marzo AM *et al*: **FASN Gene Methylation is Associated with Fatty Acid Synthase Expression and Clinical-genomic Features of Prostate Cancer**. *Cancer Research Communications* 2024, **4**(1):152–163. doi:10.1158/2767-9764.CRC-23-0248:
61. Xu H, Chen Y, Gu M, Liu C, Chen Q, Zhan M, Wang Z: **Fatty Acid Metabolism Reprogramming in Advanced Prostate Cancer**. In: *Metabolites*. vol. 11; 2021: 765.
62. Wang W, Bai L, Li W, Cui J: **The Lipid Metabolic Landscape of Cancers and New Therapeutic Perspectives**. *Frontiers in Oncology* 2020, **Volume 10 - 2020**.
63. Lai X, Liang Y, Jin J, Zhang H, Wu Z, Li G, Wang J, Zhang Z, Chen H, Zeng F *et al*: **Protein kinase C epsilon promotes de novo lipogenesis and tumor growth in prostate cancer cells by regulating the phosphorylation and nuclear translocation of pyruvate kinase isoform M2**. *Experimental Cell Research* 2023, **422**(1):113427. doi:https://doi.org/10.1016/j.yexcr.2022.113427:
64. Guerra B, Recio C, Aranda-Tavío H, Guerra-Rodríguez M, García-Castellano JM, Fernández-Pérez L: **The Mevalonate Pathway, a Metabolic Target in Cancer Therapy**. *Frontiers in Oncology* 2021, **Volume 11 - 2021**.
65. Morales A, Greenberg M, Nardi F, Gil V, Hayward SW, Crawford SE, Franco OE: **Loss of ephrin B2 receptor (EPHB2) sets lipid rheostat by regu-**

lating proteins DGAT1 and ATGL inducing lipid droplet storage in prostate cancer cells. *Laboratory Investigation* 2021, **101**(7):921–934. doi:https://doi.org/10.1038/s41374-021-00583-9:

66. Zhang Y, Wang X, Wang J, Ma K, Jia L, Liu B, Yuan X, Li Q, Wang Q, Li Q *et al*: **STARD4 suppresses tumorigenesis and attenuates enzalutamide resistance via lipid metabolic reprogramming and AR stabilization in prostate cancer**. *Journal of Experimental & Clinical Cancer Research* 2025, **44**(1):318. doi:10.1186/s13046-025-03600-7:
67. Xu H, Li S, Sun Y, Xu L, Hong X, Wang Z, Hu H: **ELOVL5-Mediated Long Chain Fatty Acid Elongation Contributes to Enzalutamide Resistance of Prostate Cancer**. In: *Cancers.* vol. 13; 2021: 3957.
68. Liu S, Zhang D, Jiang C, Chen X, Jin L, Xin S, Sun X: **SOX8/CPT2 axis regulates lipid metabolism to support enzalutamide resistance in prostate cancer**. *Cancer Cell International* 2026, **26**(1):130. doi:10.1186/s12935-026-04215-4:
69. Lounis MA, Péant B, Leclerc-Desaulniers K, Ganguli D, Daneault C, Ruiz M, Zoubeidi A, Mes-Masson A-M, Saad F: **Modulation of de Novo Lipogenesis Improves Response to Enzalutamide Treatment in Prostate Cancer**. In: *Cancers.* vol. 12; 2020: 3339.
70. Pavlova NN, Zhu J, Thompson CB: **The hallmarks of cancer metabolism: Still emerging**. *Cell Metabolism* 2022, **34**(3):355–377. doi:10.1016/j.cmet.2022.01.007:
71. DeBerardinis RJ, Chandel NS: **Fundamentals of cancer metabolism**. *Science Advances*, **2**(5):e1600200. doi:10.1126/sciadv.1600200:
72. Semenza GL: **HIF-1 and mechanisms of hypoxia sensing**. *Current Opinion in Cell Biology* 2001, **13**(2):167–171. doi:https://doi.org/10.1016/S0955-0674(00)00194-0:
73. Schito L, Semenza GL: **Hypoxia-Inducible Factors: Master Regulators of Cancer Progression**. *Trends in Cancer* 2016, **2**(12):758–770. doi:https://doi.org/10.1016/j.trecan.2016.10.016:
74. Ippolito L, Morandi A, Giannoni E, Chiarugi P: **Lactate: A Metabolic Driver in the Tumour Landscape**. *Trends in Biochemical Sciences* 2019, **44**(2):153–166. doi:https://doi.org/10.1016/j.tibs.2018.10.011:
75. Cutruzzolà F, Giardina G, Marani M, Macone A, Paiardini A, Rinaldo S, Paone A: **Glucose Metabolism in the Progression of Prostate Cancer**. *Frontiers in Physiology* 2017, **Volume 8 - 2017**.
76. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, Arora VK, Kaushik P, Cerami E, Reva B *et al*: **Integrative Genomic Profiling of Human Prostate Cancer**. *Cancer Cell* 2010, **18**(1):11–22. doi:10.1016/j.ccr.2010.05.026:
77. Sun R, Huang Y, He H, Li Q, Wang L, Zhang G, Wei Z, Cao Y, Li J, Wang X *et al*: **KDM5B-driven glucose metabolic reprogramming promotes enzalutamide resistance in prostate cancer via the lactate/hnRNPA1 lactylation/AR-V7 axis**. *Molecular Cancer* 2026, **25**(1):67. doi:10.1186/s12943-026-02602-z:
78. Chetta P, Sriram R, Zadra G: **Lactate as Key Metabolite in Prostate Cancer Progression: What Are the Clinical Implications?** In: *Cancers.* vol. 15; 2023: 3473.
79. Li L, Luo J, Zhao L, Tian L, Wang J, Cheng Y, Li X: **Methylation-induced silencing of AZGP1 enhances prostate cancer metastasis by stimulating tumoral glycolysis**. *Cellular & Molecular Biology Letters* 2026, **31**(1):5. doi:10.1186/s11658-025-00818-3:
80. Winther MD, Kristensen G, Stroomberg HV, Berg KD, Toft BG, Brooks JD, Brasso K, Røder MA: **AZGP1 Protein Expression in Hormone-Naïve Advanced Prostate Cancer Treated with Primary Androgen Deprivation Therapy**. In: *Diagnostics.* vol. 10; 2020: 520.
81. Wen RM, Qiu Z, Marti GEW, Peterson EE, Marques FJG, Bermudez A, Wei Y, Nolley R, Lam N, Polasko AL *et al*: **AZGP1 deficiency promotes angiogenesis in prostate cancer**. *Journal of Translational Medicine* 2024, **22**(1):383. doi:10.1186/s12967-024-05183-x:
82. Alcon-Rodriguez S, Mayo JC, Gonzalez-Menendez P, Fernandez-Vega I, Hevia D, Fernandez-Vega S, Moran-Alvarez A, Pineda-Cevallos D, Alvarez-Mugica M, Rodriguez-Gonzalez P *et al*: **TXNIP upregulation controls metabolism and cell cycle during androgen deprivation therapy in prostate cancer**. *Cell Death & Disease* 2025, **16**(1):817. doi:10.1038/s41419-025-08128-4:
83. Sun X, Zhang Y, Zhang W, Jin L, Xin S: **Targeting NXPH4/ALDH1L2 signaling suppresses enzalutamide resistance in prostate cancer**. *Cell Death Discovery* 2026, **12**(1):91. doi:10.1038/s41420-026-02944-z:
84. Shao Y, Ye G, Ren S, Piao H-L, Zhao X, Lu X, Wang F, Ma W, Li J, Yin P *et al*: **Metabolomics and transcriptomics profiles reveal the dysregulation of the tricarboxylic acid cycle and**

related mechanisms in prostate cancer. *International Journal of Cancer* 2018, **143**(2):396–407. doi:https://doi.org/10.1002/ijc.31313:

85. Ghoneum A, Abdulfattah AY, Warren BO, Shu J, Said N: **Redox Homeostasis and Metabolism in Cancer: A Complex Mechanism and Potential Targeted Therapeutics**. In: *International Journal of Molecular Sciences*. vol. 21; 2020: 3100.
86. Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat J-P, White TA, Stojanov P, Van Allen E, Stransky N *et al*: **Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer**. *Nature Genetics* 2012, **44**(6):685–689. doi:10.1038/ng.2279:
87. Takeda DY, Spisák S, Seo J-H, Bell C, O'Connor E, Korthauer K, Ribli D, Csabai I, Solymosi N, Szállási Z *et al*: **A Somatically Acquired Enhancer of the Androgen Receptor Is a Noncoding Driver in Advanced Prostate Cancer**. *Cell* 2018, **174**(2):422–432.e413. doi:https://doi.org/10.1016/j.cell.2018.05.037:
88. Adams EJ, Karthaus WR, Hoover E, Liu D, Gruet A, Zhang Z, Cho H, DiLoreto R, Chhangawala S, Liu Y *et al*: **FOXA1 mutations alter pioneering activity, differentiation and prostate cancer phenotypes**. *Nature* 2019, **571**(7765):408–412. doi:10.1038/s41586-019-1318-9:
89. Parolia A, Cieslik M, Chu S-C, Xiao L, Ouchi T, Zhang Y, Wang X, Vats P, Cao X, Pitchiaya S *et al*: **Distinct structural classes of activating FOXA1 alterations in advanced prostate cancer**. *Nature* 2019, **571**(7765):413–418. doi:10.1038/s41586-019-1347-4:
90. Asangani IA, Dommeti VL, Wang X, Malik R, Cieslik M, Yang R, Escara-Wilke J, Wilder-Romans K, Dhanireddy S, Engelke C *et al*: **Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer**. *Nature* 2014, **510**(7504):278–282. doi:10.1038/nature13229:
91. Welti J, Sharp A, Yuan W, Dolling D, Nava Rodrigues D, Figueiredo I, Gil V, Neeb A, Clarke M, Seed G *et al*: **Targeting Bromodomain and Extra-Terminal (BET) Family Proteins in Castration-Resistant Prostate Cancer (CRPC)**. *Clinical Cancer Research* 2018, **24**(13):3149–3162. doi:10.1158/1078-0432.CCR-17-3571:
92. Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, Goodrich MM, Labbé DP, Gomez EC, Wang J *et al*: **Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance**. *Science* 2017, **355**(6320):78–83. doi:10.1126/science.aah4199:
93. Mu P, Zhang Z, Benelli M, Karthaus WR, Hoover E, Chen C-C, Wongvipat J, Ku S-Y, Gao D, Cao Z *et al*: **SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer**. *Science* 2017, **355**(6320):84–88. doi:10.1126/science.aah4307:
94. Detassis S, Precazzini F, Grasso M, Del Vescovo V, Maines F, Caffo O, Campomenosi P, Denti MA: **Plasma microRNA Signature as Companion Diagnostic for Abiraterone Acetate Treatment in Metastatic Castration-Resistant Prostate Cancer: A Pilot Study**. In: *International Journal of Molecular Sciences*. vol. 25; 2024: 5573.
95. Halabi S, Guo S, Park JJ, Nanus DM, George DJ, Antonarakis ES, Danila DC, Szmulewitz RZ, McDonnell DP, Norris JD *et al*: **The Impact of Circulating Tumor Cell HOXB13 RNA Detection in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Abiraterone or Enzalutamide**. *Clinical Cancer Research* 2024, **30**(6):1152–1159. doi:10.1158/1078-0432.CCR-23-3017:
96. Zou M, Toivanen R, Mitrofanova A, Floch N, Hayati S, Sun Y, Le Magnen C, Chester D, Mostaghel EA, Califano A *et al*: **Transdifferentiation as a Mechanism of Treatment Resistance in a Mouse Model of Castration-Resistant Prostate Cancer**. *Cancer Discovery* 2017, **7**(7):736–749. doi:10.1158/2159-8290.CD-16-1174:
97. Maasoumyhaghighi H, Nouri M, Liu J, Liu X: **Molecular mechanisms driving lineage plasticity in prostate cancer: NANOG and beyond**. *Cancer Heterogeneity and Plasticity* 2025, **2**(1):0001.
98. Dardenne E, Beltran H, Benelli M, Gayvert K, Berger A, Puca L, Cyrta J, Sboner A, Noorzad Z, MacDonald T *et al*: **N-Myc Induces an EZH2-Mediated Transcriptional Program Driving Neuroendocrine Prostate Cancer**. *Cancer Cell* 2016, **30**(4):563–577. doi:https://doi.org/10.1016/j.ccell.2016.09.005:
99. Lee JK, Phillips JW, Smith BA, Park JW, Stoyanova T, McCaffrey EF, Baertsch R, Sokolov A, Meyerowitz JG, Mathis C *et al*: **N-Myc Drives Neuroendocrine Prostate Cancer Initiated**

from Human Prostate Epithelial Cells. *Cancer Cell* 2016, **29**(4):536–547. doi:https://doi.org/10.1016/j.ccell.2016.03.001:

100. Bishop JL, Thaper D, Vahid S, Davies A, Ketola K, Kuruma H, Jama R, Nip KM, Angeles A, Johnson F *et al*: **The Master Neural Transcription Factor BRN2 Is an Androgen Receptor–Suppressed Driver of Neuroendocrine Differentiation in Prostate Cancer**. *Cancer Discovery* 2017, **7**(1):54–71. doi:10.1158/2159-8290.CD-15-1263:
101. Chan JM, Zaidi S, Love JR, Zhao JL, Setty M, Wadosky KM, Gopalan A, Choo Z-N, Persad S, Choi J *et al*: **Lineage plasticity in prostate cancer depends on JAK/STAT inflammatory signaling**. *Science* 2022, **377**(6611):1180–1191. doi:10.1126/science.abn0478:
102. Rubin MA, Bristow RG, Thienger PD, Dive C, Imielinski M: **Impact of Lineage Plasticity to and from a Neuroendocrine Phenotype on Progression and Response in Prostate and Lung Cancers**. *Molecular Cell* 2020, **80**(4):562–577. doi:https://doi.org/10.1016/j.molcel.2020.10.033:
103. Storck WK, May AM, Westbrook TC, Duan Z, Morrissey C, Yates JA, Alumkal JJ: **The Role of Epigenetic Change in Therapy-Induced Neuroendocrine Prostate Cancer Lineage Plasticity**. *Frontiers in Endocrinology* 2022, **Volume 13 - 2022**.
104. Davies A, Conteduca V, Zoubeidi A, Beltran H: **Biological Evolution of Castration-resistant Prostate Cancer**. *European Urology Focus* 2019, **5**(2):147–154. doi:https://doi.org/10.1016/j.euf.2019.01.016:
105. Cheng S, Yang S, Shi Y, Shi R, Yeh Y, Yu X: **Neuroendocrine prostate cancer has distinctive, non-prostatic HOX code that is represented by the loss of HOXB13 expression**. *Scientific Reports* 2021, **11**(1):2778. doi:10.1038/s41598-021-82472-1:
106. Imamura J, Ganguly S, Muskara A, Liao RS, Nguyen JK, Weight C, Wee CE, Gupta S, Mian OY: **Lineage plasticity and treatment resistance in prostate cancer: the intersection of genetics, epigenetics, and evolution**. *Frontiers in Endocrinology* 2023, **Volume 14 - 2023**.
107. Ersoy-Fazlioglu B, Lingadahalli S, Altintas UB, Cingoz A, Tekoglu E, Lok Yu IP, Dikbas M, Missaghimamaghani O, Yavuz K, Adomat H *et al*: **Distinct transcription factor interactions drive HOXB13 activity in different stages of prostate cancer**. *Proceedings of the National Academy of Sciences* 2025, **122**(49):e2500327122. doi:10.1073/pnas.2500327122:
108. Angappulige DH, Mahajan NP, Mahajan K: **Epigenetic underpinnings of tumor-immune dynamics in prostate cancer immune suppression**. *Trends in Cancer* 2024, **10**(4):369–381. doi:https://doi.org/10.1016/j.trecan.2024.01.004:
109. Raith F, O'Donovan DH, Lemos C, Politz O, Haendler B: **Addressing the Reciprocal Crosstalk between the AR and the PI3K/AKT/mTOR Signaling Pathways for Prostate Cancer Treatment**. In: *International Journal of Molecular Sciences*. vol. 24; 2023: 2289.
110. Cui Z, Huang F, Fang K, Yan J, Zhang Y, Kang DD, Zhou Y, Zhao Y, Everitt JI, Hankey W *et al*: **SCORT–Cas13d Nanotherapy Precisely Targets the 'Undruggable' Transcription Factor HoxB13 in Metastatic Prostate Cancer In Vivo**. *Advanced Science* 2025, **12**(23):2417605. doi:https://doi.org/10.1002/advs.202417605: