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Metabolic Reprogramming in Prostate Cancer: The Roles of HOXB13 and FASN in Tumor Progression and Therapy

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ABSTRACT

Metabolic reprogramming, particularly lipid metabolism, is a hallmark of cancer progression and a critical vulnerability in prostate cancer (PCa). Two pivotal studies, one by Lu et al. and the other by Dairo et al., have illuminated the roles of HOXB13, a transcriptional regulator, and fatty acid synthase (FASN), a key enzyme in lipid biosynthesis, in the metabolic dysregulation of PCa. The Lu et al. study highlights HOXB13's role in androgen receptor (AR)-independent PCa, where it regulates lipid metabolism via epigenetic mechanisms involving histone deacetylase HDAC3. A G84E mutation in HOXB13 disrupts this regulation, leading to increased lipid synthesis and a pro-metastatic phenotype. The Dairo et al. study demonstrates that FASN hypomethylation, coupled with increased expression, drives lipid biosynthesis critical for tumor growth. Both studies establish a link between HOXB13 mutations and FASN dysregulation, underscoring their interplay in PCa biology. Therapeutically, pharmacological inhibition of FASN mitigates the aggressive features of HOXB13-deficient or mutant PCa, highlighting lipid metabolism as a promising target. Despite their strengths, including robust methodologies, limitations include reliance on preclinical models and the need for broader patient diversity. These studies collectively emphasize the potential of metabolic and epigenetic interventions for precision medicine in PCa, paving the way for novel therapies targeting lipid metabolism in patients with specific genetic and epigenetic profiles.

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Main Commentary

The interplay between metabolic reprogramming, genetic alterations, and epigenetic modifications is increasingly recognized as a cornerstone of cancer biology. Lipid metabolism, in particular, is essential for tumor growth, providing energy and structural components for rapidly dividing cells, making it a key vulnerability in cancers such as prostate cancer (PCa) [1, 2]. Understanding the intricate relationship between altered lipid metabolism and PCa development and progression represents a critical avenue for uncovering the disease's biology and identifying therapeutic opportunities. Notably, the accumulation of lipid droplets in aggressive PCa tumors underscores the central role of lipid metabolic reprogramming in driving tumor aggressiveness and adaptation [3, 4].

Fatty acid synthase (FASN), a pivotal enzyme in de novo lipogenesis, emerges as a key player in this process. Its overexpression in PCa tissues, correlating with higher Gleason scores, highlights its biomarker potential and suggests a direct link between lipogenesis and tumor severity [5, 6]. The tight regulation of lipogenic enzymes through transcriptional and post-translational modifications reflects the importance of lipid metabolism in maintaining energy balance within tumor cells, an adaptation to their heightened metabolic demands.

The androgen receptor (AR) adds another layer of complexity by modulating lipid synthesis, uptake, and utilization. The reactivation of AR-driven lipid biosynthesis in metastatic castration-resistant prostate cancer (mCRPC) exemplifies the interplay between androgen signaling and lipid metabolism in tumor progression [7, 8]. Despite these insights, significant gaps remain in understanding the molecular mechanisms driving enhanced lipogenesis and lipid storage in PCa. Unraveling these mechanisms could lead to the development of targeted therapies that exploit the vulnerabilities of lipid metabolic pathways in PCa.

Table 1: Summary of critical findings of Lu and Dairo studies.

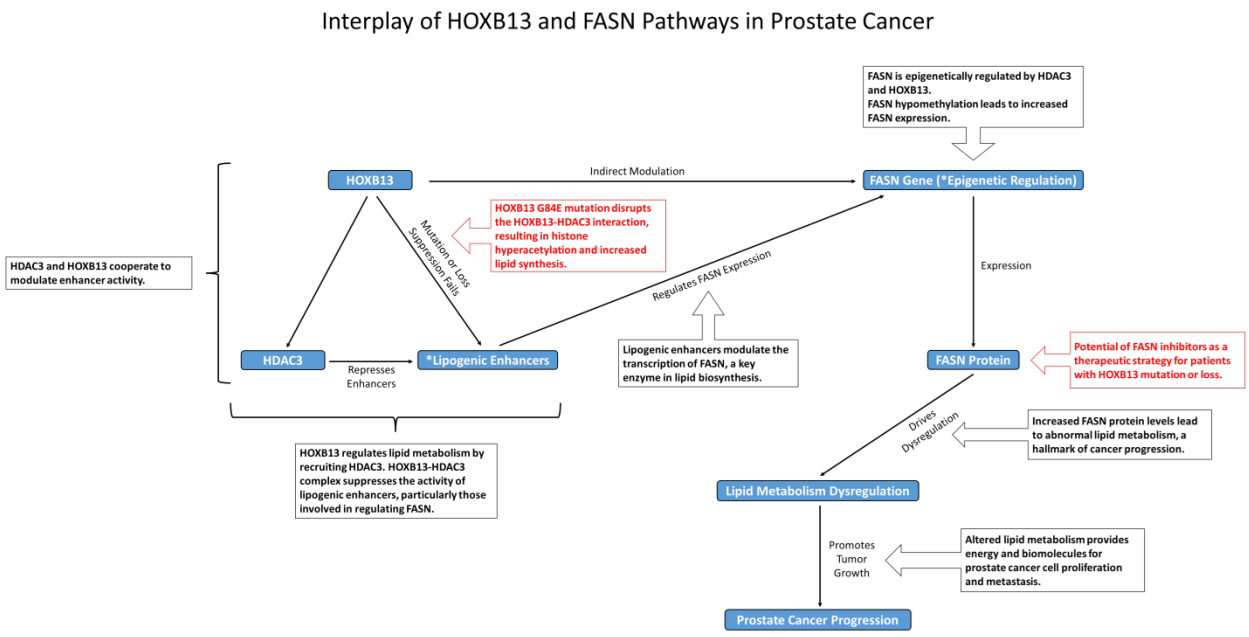
Aspect	Lu et al. [9]	Dairo et al. [10]
Key Mechanism	HOXB13 recruits HDAC3 to suppress de novo lipogenesis in prostate cancer cells.	FASN gene hypomethylation correlates with increased FASN expression in prostate cancer.
Mutation/Deficiency Effects	HOXB13 loss or G84E mutation causes lipid accumulation, promoting metastasis.	Tumors with the HOXB13 G84E mutation show increased FASN expression.
Epigenetic Regulation	HOXB13 regulates lipid metabolism via HDAC3-mediated epigenetic reprogramming.	FASN gene body methylation inversely correlates with FASN expression and protein levels.
Associated Genes	Mutations in HOXB13 directly affect lipid metabolism pathways.	ERG gene rearrangement is associated with increased FASN expression and hypomethylation.
Therapeutic Implications	Lipogenic pathway inhibitors, like fatty acid synthase inhibitors, may mitigate metastatic effects.	FASN hypomethylation may serve as a biomarker to select patients for trials of FASN inhibitors.
Race Association	Not discussed.	No significant association between FASN expression/methylation and self-identified race across cohorts.
Clinical Significance	Highlights HOXB13's critical role in prostate cancer lipid metabolism and metastasis regulation.	Identifies FASN methylation as a key epigenetic regulator and a potential biomarker in prostate cancer treatment.

Two pivotal studies - one by Lu et al. [9] focusing on the transcriptional regulator HOXB13 and another by Dairo et al. [10] on the metabolic enzyme FASN - offer complementary insights into the metabolic dysregulation in PCa. Together, these studies underscore the critical role of lipid metabolism in cancer progression and provide a framework for novel therapeutic strategies. Table 1 summarizes the critical findings of both studies.

The Lu et al. study explores the role of HOXB13, a homeodomain transcription factor, in PCa progression, particularly under androgen receptor (AR)-independent conditions. Traditionally associated with AR signaling and androgen-dependent growth [11], HOXB13 is revealed to mediate epigenetic regulation of lipid metabolism by recruiting histone deacetylase HDAC3. This complex suppresses lipogenic enhancers, particularly those regulating FASN, a key enzyme in de novo lipogenesis. The HOXB13 G84E mutation, linked to early-onset PCa [11, 12], disrupts the HOXB13-HDAC3 interaction, leading to histone hyperacetylation, increased lipid synthesis, and a pro-metastatic cellular environment. The study also identifies hypermethylation and downregulation of HOXB13 in mCRPC, emphasizing its potential as a biomarker for disease progression. Importantly, pharmacological inhibition of FASN mitigated aggressive characteristics in HOXB13-deficient or G84E-mutant PCa models, underscoring the therapeutic potential of targeting lipogenic pathways.

The Dairo et al. study examines the epigenetic and clinical-genomic aspects of FASN in PCa. Using advanced profiling techniques like InfiniumEPIC and whole-genome bisulfite sequencing, the study identifies FASN hypomethylation as a hallmark of primary and metastatic prostate tumors, strongly associated with increased FASN expression at both RNA and protein levels. FASN expression is linked to HOXB13 G84E mutations, suggesting a role for HOXB13 in regulating FASN epigenetically. Tumors with ERG gene rearrangement also exhibited increased FASN expression, representing a molecular subtype of PCa reliant on enhanced lipid synthesis. However, this study found no significant association between FASN methylation/expression and race when ERG status was considered. This finding contrasts with reports of increased lipid synthesis in African American patients [13-15], suggesting that FASN may not be the primary regulator or target for lipid synthesis in this population. Possible explanations for this discrepancy include population-specific differences in lipid metabolic pathways, alternative regulators of lipid metabolism, or limitations in study design. Further research is needed to clarify these dynamics.

Figure 1: Interplay of HOXB13 and FASN pathways in prostate cancer.



Lipogenic Enhancers: Specific DNA sequences within the genome that increase transcription of lipid metabolism-related genes.
Epigenetic Regulation: Process of controlling gene activity without altering the underlying DNA sequence itself, achieved through modifications like DNA methylation or histone modifications

Both studies highlight the importance of lipid metabolism in PCa progression and identify HOXB13 and FASN as central regulators (Figure 1). Lu et al. shows how HOXB13 dysfunction drives enhanced lipogenesis and tumor aggressiveness, while Dairo et al. validates these findings by linking HOXB13 and FASN expression in patient samples. This alignment between laboratory and patient-derived data underscores the utility of experimental models for studying PCa. Together, they establish FASN as a potential therapeutic target, particularly for tumors with HOXB13 G84E mutations or ERG rearrangements. Table 2 highlights the roles, methods, and therapeutic implications of HOXB13 and FASN.

HOXB13 is a well-established pioneer factor known for regulating *FOXA1* and the chromatin binding and activity of AR [16]. Given that most PCa, including CRPC, remain AR-dependent, HOXB13 appears to play dual roles in lipid metabolism and cancer progression. First, HOXB13 can repress the expression of FASN and other lipid-related genes through an AR-independent mechanism, potentially acting as a negative regulator in specific cellular contexts. Second, it can stimulate the expression of FASN and other lipid-associated genes via an AR-dependent mechanism, reinforcing the critical role of AR signaling in driving lipid metabolism and tumor growth [11]. This dual functionality highlights a complex interplay between AR signaling and lipid metabolism, positioning HOXB13 as a pivotal modulator in PCa progression. Understanding these distinct mechanisms could provide valuable insights into how HOXB13 influences metabolic reprogramming in PCa and may reveal novel therapeutic opportunities targeting both AR-dependent and AR-independent pathways.

Translating these findings into clinical practice presents challenges. Developing FASN inhibitors has faced hurdles like achieving selective targeting to avoid off-tumor effects and overcoming tumor resistance mechanisms [17]. First-generation inhibitors, such as orlistat, cerulenin, and C75, showed promising anti-tumor effects but faced limitations like poor bioavailability, metabolic instability, and off-target effects, including weight loss with C75. Next-generation inhibitors, including C93, IPI-9119, and TVB-2640, offer greater specificity and reduced toxicity. Notably, TVB-2640 has advanced to clinical trials, including phase II studies for HER2-positive breast cancer in combination therapies, highlighting its therapeutic potential [18]. Advances in drug design, such as more selective FASN inhibitors and combination therapies,

Table 2: Comparison between HOXB13 and FASN in multiple parameters.

Aspect	HOXB13	Fatty acid synthase (FASN)
Biological Role	• Homeobox gene encoding a transcription factor.	• Key enzyme involved in de novo lipogenesis.
	• Plays a critical role in development, prostate cancer progression, and hormonal regulation.	• Catalyzes the synthesis of long-chain fatty acids, crucial for energy storage and cell membrane synthesis.
	• Regulates genes related to differentiation and oncogenesis.	• Overexpressed in cancer, providing substrates for proliferation.
Experimental Methodologies	• **Gene expression profiling**: RNA-seq and qPCR to measure HOXB13 expression across tissues and disease states.	• **Enzymatic activity assays**: Colorimetric or fluorometric assays to quantify FASN catalytic activity.
	• **Chromatin immunoprecipitation (ChIP)**: Identifies DNA sequences bound by HOXB13 in regulatory networks.	• **Western blot and IHC**: Used to measure FASN expression in normal and cancer tissues.
	• **Gene knockout/knockdown models**: CRISPR-Cas9 or siRNA used in cell lines and animal models to assess HOXB13 function.	• **Inhibitor studies**: Small molecules like **C75**, **Orlistat**, and natural compounds to test FASN inhibition effects.
	• **Protein-protein interaction studies**: Co-immunoprecipitation assays for studying interaction with AR and other factors.	• **Metabolic tracing**: Using isotopically labeled precursors (e.g., [13C]-glucose) to study lipid synthesis.
	• **Reporter assays**: Evaluate HOXB13's role in promoter activity regulation.	• **High-resolution mass spectrometry**: Quantifies lipid profiles altered by FASN overexpression.
Therapeutic Implications	• Target for prostate cancer therapy (e.g., AR/HOXB13 interaction modulators).	• Target for metabolic disorders and cancer (FASN inhibitors).
	• HOXB13 mutations (e.g., G84E) associated with prostate cancer risk.	• FASN overexpression linked to poor prognosis in cancers like breast, prostate, and ovarian [25].
	• Potential prognostic biomarker in prostate cancer [26].	• FASN inhibitors show promise in preclinical models of cancer therapy.

are critical. Additionally, patient stratification based on genetic, epigenetic, and metabolic profiling is essential to identify those most likely to benefit. Biomarkers such as HOXB13 mutations, ERG rearrangements, or FASN methylation status can guide patient stratification and personalized therapies.

The findings from these studies align with broader trends in cancer metabolism research, supporting lipid metabolism inhibitors as promising therapeutic strategies [19-21]. Similar vulnerabilities have been exploited in other cancers, such as targeting glutamine metabolism in glioblastoma [22], glycolysis in colorectal cancer [23], and fatty acid synthesis in oncogenic KRAS-mediated lung adenocarcinoma, hepatocellular carcinoma, and glioblastoma [24]. The identification of FASN and HOXB13 as critical players in PCa metabolism underscores the potential of targeting lipid metabolic pathways across various tumor types. Moreover, these studies contribute to the growing emphasis on integrating multi-omic data to uncover actionable targets and develop precision therapies. The potential application of FASN inhibitors in PCa could mirror the success of PARP inhibitors in *BRCA*-mutated cancers, showcasing the power of treatments tailored to a patient's unique genetic and molecular profile [25, 26].

Despite their contributions, both studies have limitations. Lu et al.'s reliance on preclinical models

and lack of patient diversity may limit the generalizability of its findings. Dairo et al.'s focus on a single pathway of FASN methylation and absence of functional studies, such as knockout or knock-in models, restricts understanding of broader systemic interactions. The reliance on complex profiling techniques poses challenges for immediate clinical application, underscoring the need for accessible diagnostic tools and validation in diverse clinical contexts.

Future research should explore the broader regulatory network linking HOXB13 and FASN, integrating metabolic, genetic, and epigenetic data. Functional studies to elucidate the direct biological effects of FASN methylation and the development of combination therapies targeting metabolic and epigenetic pathways hold promise. Stratifying patients by treatment history, disease stage, and genetic alterations could provide deeper insights into the role of lipid metabolism in PCa and refine therapeutic strategies.

The findings from Lu et al. and Dairo et al. represent significant advancements in understanding lipid metabolism's role in PCa. HOXB13 dysfunction and FASN dysregulation emerge as critical drivers of tumor progression, offering biomarkers and therapeutic targets for precision medicine. By elucidating the metabolic vulnerabilities of PCa, these studies pave the way for more effective and personalized treatments, with FASN inhibitors and epigenetic modulators at the forefront of therapeutic development.

Disclosures

The authors have no conflicts of interest.

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